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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 243/08, 295/14, 295/08, 295/06, 401/06, 405/06, 403/06, A61K 31/495

A1

(11) International Publication Number: WO 97/44329

(43) International Publication Date: 27 November 1997 (27.11.97)

(21) International Application Number: PCT/US97/08577

(22) International Filing Date: 20 May 1997 (20.05.97)

(30) Priority Data:

8/147846	20 May 1996 (20.05.96)	JP
08/858, 238	19 May 1997 (19.05.97)	US

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(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

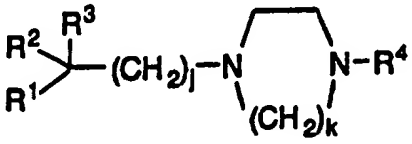
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DIARYLALKYL CYCLIC DIAMINE DERIVATIVES AS CHEMOKINE RECEPTOR ANTAGONISTS

(57) Abstract

Cyclic diamines of formula (I) or their pharmacologically acceptable acid addition salts, and their medical applications are described. These compounds inhibit the action of chemokines such as MIP-1a and/or MCP-1 on target cells, and are useful as a therapeutic drug and/or preventative drug in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissues.



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SPECIFICATION

DIARYLALKYL CYCLIC DIAMINE DERIVATIVES AS CHEMOKINE RECEPTOR ANTAGONISTS

Technical field

This invention relates to novel diarylalkyl cyclic diamine derivatives.

This invention also relates to chemokine receptor antagonists that may be effective as a therapeutic agent and/or preventive agent for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, glomerulonephritis, multiple sclerosis, pulmonary fibrosis, and myocarditis, in which tissue infiltration of blood monocytes and lymphocytes plays a major role in the initiation, progression or maintenance of the disease.

Background Technology

Chemokines are a group of inflammatory/immunomodulatory polypeptide factors produced by lymphatic tissues and by activated macrophages and leukocytes at inflammatory sites; they have a molecular weight of 6-15 kD, contain four cysteine residues, are basic and have heparin binding activity. The chemokines can be classified into two subfamilies, the CXC chemokines and CC chemokines, by the common location of the four cysteine residues and by the differences in the chromosomal locations of the genes encoding them. For example IL-8 (abbreviation for interleukin-8 is a CXC chemokine, while the CC chemokines include MIP-1α/β (abbreviation for macrophage inflammatory protein-1α/β), MCP-1 (abbreviation for monocyte chemotactic protein-1), and RANTES (abbreviation for regulated on activation, normal T-cell expressed and secreted cytokine). There also exists a chemokine called lymphotactin, which does not fall into either chemokine subfamily. These chemokines promote cell migration, increase the expression of cellular adhesion molecules such as integrins, and promote cellular adhesion, and are thought to be the protein factors intimately involved in the adhesion and infiltration of leukocytes into the pathogenic sites in such as inflammatory tissues (for references, see for example, Michiel, D., Biotechnology, 1993, 11, 739; Oppenheim, J.J., et al., Annual Review of Immunology, 1991, 9, 617-648; Schall, T.J., Cytokine, 1991, 3, 165-183; Springer, T.A., Cell, 1994, 76, 301-314; Furie, M.B., American Journal of Path logy, 1995,

146, 1287-1301; Keln r, G.S., et al., Science, 1994, 266, 1395-1399).

For example, MIP-1α induces cell migration and causes a transient increase in intracellular calcium ion concentration levels, an increase in the expression of integrins, adhesion molecules, and degranulation of monocytes and lymphocytes, and inhibits bone marrow stem cell proliferation (See for example, Wolpe, S.D., et al., Journal of Experimental Medicine, 1988, 167, 570-581; Wolpe, S.D., et al., Faseb Journal, 1989, 3, 2565-2573; Taub, D.D., et al., Science, 1993, 260, 355-358; Schall, T.J., et al., Journal of Experimental Medicine, 1993, 177, 1821-1825; Neote, K., et al., Cell, 1993, 72, 415-425; Vaddi, K., et al., The Journal of Immunology, 1994, 153, 4721-4732).

With respect to the activity of MIP-1α in vivo and its role in the pathogenesis of disease, it has been reported that it is a pyrogen in rabbits (see for example Davatelis, G., et al., Science, 1989, 243, 1066-1068); that MIP-1α injection into mouse foot pads results in an inflammatory reaction such as infiltration by neutrophils and mononuclear cells (see for example Alam, R., et al., The Journal of Immunology, 1994, 152, 1298-1303); that MIP-1α neutralizing antibody has an inhibitory effect or a therapeutic effect in animal models of granuloma, multiple sclerosis and idiopathic pulmonary fibrosis (see for example Lukacs, N.W., et al., Journal of Experimental Medicine, 1993, 177, 1551-1559; Kaprus, W.J., et al., The Journal of Immunology, 1995, 155, 5003-5010; Smith, R.E., et al., The Journal of Immunology, 1994, 153, 4704-4712); and that coxsackie virus induced myocarditis is inhibited in mice with a disrupted MIP-1α gene (see for example Cook, D.N. et al., Science, 1995, 269, 1583-1585). These studies indicate that MIP-1α is deeply involved in the local attraction of various subtypes of leukocytes and the initiation, progression and maintenance of resulting inflammatory response.

MCP-1 (also known as MCAF (abbreviation for macrophage chemotactic and activating factor) or JE) is a chemokine produced by macrophages, smooth muscle cells, fibroblasts, and vascular endothelial cells and causes cell migration and cell adhesion of monocytes, memory T cells, and natural killer cells, as well as mediating histamine release by basophils (For reference, see for example, Rollins, B.J., et al., Proc. Natl. Acad. Sci. USA, 1988, 85, 3738-3742; Matsushima, K., et al., Journal of Experimental Medicine, 1989, 169, 1485-1490; Yoshimura, T. et al., Febs Letters, 1989, 244, 487-493; Rollins, B.J. t al., Blood, 1991, 78, 1112-1116; Carr, M.W., et al., Proc. Natl. Acad. Sci. USA, 1994, 91,

3652-3656; Jiang, Y., et al., American Journal of Physiology, 1994, 267, C1112-C1118; Allavena, P., et al., European Journal of Immunology, 1994, 24, 3233-3236; Alam, R., et al., The Journal of Clinical Investigation, 1992, 89, 723-728).

In addition, high expression of MCP-1 has been reported in diseases where accumulation of monocyte/macrophage and/or T cells is thought to be important in the initiation or progression of diseases, such as atherosclerosis, restenosis due to endothelial injury following angioplasty, rheumatoid arthritis, glomerulonephritis, pulmonary fibrosis, asthma and psoriasis (for reference, see for example, Firestein, G.S. et al., Arthritis and Rheumatism, 1990, 33, 768-773; Nikolic-Peterson, D.J., et al., Kidney International, 1994, 45, enlarged ed., 45, S79-S82; Thomas, P.D., et al., American Review of Respiratory Disease, 1987, 135, 747-760; Ross, R., Nature, 1993, 362, 801-809; Cooper, K.D., et al., The Journal of Investigative Dermatology, 1994, 102, 128-137; Sousa, A.R., et al., American Journal of Respiratory Cell And Molecular Biology, 1994). Furthermore, anti-MCP-1 antibody has been reported to inhibit delayed type hypersensitivity and hepatitis (for reference, see for example Rand, M.L., et al., American Journal of Pathology, 1996, 148, 855-864; Wada, T., et al., Faseb Journal, 1996, 10, 1418-1425).

These data indicate that chemokines such as MIP-1α and MCP-1 attract monocytes and lymphocytes to disease sites and mediate their activation and thus are thought to be intimately involved in the initiation, progression and maintenance of diseases deeply involving monocytes and lymphocytes, such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, glomerulonephritis, multiple sclerosis, pulmonary fibrosis and myocarditis.

Therefore, drugs which inhibit the action of chemokines on target cells may be effective as a therapeutic and/or preventive drug in diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, glomerulonephritis, multiple sclerosis, pulmonary fibrosis, and myocarditis.

Genes encoding receptors of specific chemokines have been cloned, and it is now known that these receptors are G protein-coupled seven-transmembrane receptors present on various leukocyte populations (for reference, see for example, Holmes, W.E., et al., Science 1991, 253, 1278-1280; Murphy P.M., et al., Science, 253, 1280-1283; N ote, K. et al., Cell, 1993, 72, 415-425; Charo, I.F., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 2752-2756; Yamagami, S.,

et al., Biochem. Biophys. Res. C mmun., 1994, 202, 1156-1162; Combadier, C., et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494, Power, C.A., et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M., et al., Biochemistry, 1996, 35, 3362-3367; Murphy, P.M., Annual Review of Immunology, 1994, 12, 592-633). Therefore, compounds which inhibit the binding of chemokines such as MIP-1α and/or MCP-1 to these receptors, that is, chemokine receptor antagonists, may be useful as drugs which inhibit the action of chemokines such as MIP-1α and/or MCP-1 on the target cells, but there are no drugs known to have such effects.

Cyclic diamine derivatives containing diarylalkyl groups are known to have muscarine receptor antagonistic activity (JP09-020758, Kokai) and may be useful as a drug in the treatment of substance abuse disorders (W09320821), may potentiate the effect of anti-cancer drugs by the inhibition of P-glycoproteins (JP03-101662, Kokai; EP363212), has calcium antagonistic activity ((a) DE3831993, (b) W09013539, (c) JP63-280081, Kokai; EP289227, (d) JP62-167762, Kokai; DE3600390), have activity on the central nervous system and inhibits hypermotility (W08807528), have antiaggression, antipsychotic, antidepressant and, analgesic effect (JP57-500828, Kokai), has coronary vasodilating activity (JP51-098281, Kokai), has anti-lipidemia effect and promotes vascular blood flow (JP49-093379, Kokai; EP42366), have coronary vasodilating activity and anti-reserpine activity (Aritomi, J., et al., Yakugaku Zasshi, 1971, 91, 972-979); have anti-serotonin and anti-histamine activity (JP45-031193, Kokoku); and have central nervous system depressant activity (Vadodaria, D.J., et al., J. Med. Chem., 1969, 12, 860-865). However, these compounds differ from the novel compounds of the present invention and these compounds have not been known to interfere with binding of chemokines to the target cells.

Disclosure of the Invention

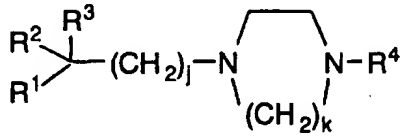
Therefore, it is an object of the present invention to discover small molecule drugs which inhibit the binding of chemokines such as MIP-1α and/or MCP-1 to their receptors on the target cells

It is another object of the present invention to establish a method to inhibit the binding to the receptors on the target cells and/or effects on target cells of chemokines such as MIP-1 α and/or MCP-1.

It is an additional object of the present invention to propose a method for the treatment of diseas s for which the binding of chemokines such as MIP-1α and/or MCP-1 to the receptor on the target cell is one of the causes.

As a result of their intensive studies, the present inventors discovered that a cyclic diamine derivative having a diarylalkyl group or its pharmacologically acceptable acid adduct has an excellent activity to inhibit the binding of chemokines such as MIP-1α and/or MCP-1 and the like to the receptor of a target cell, which has led to the completion of this invention.

That is, the present invention provides a cyclic diamine derivative or its pharmacologically acceptable acid adduct (Invention 1), represented by the formula [I] below:



[I]

[wherein R^1 and R^2 are identical to or different from each other representing a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, in which the phenyl or aromatic heterocyclic group may be substituted by any number of halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, C_1-C_6 hydroxyalkyl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoylamino groups, dioxolanyl grpoups, or by group represented by the formula: $-NR^5R^6$, or else may be condensed with a benzene ring to form a condensed ring, furthermore above substituents for the phenyl or aromatic heterocyclic group and the condenced ring condenced with a benzene ring are optionally substituted by any substituents independently selected from halogen atoms, hydroxy groups, or C_1-C_6 lower alkoxy groups, and R^5 and R^6 may be identical to or different from each other representing hydrogen atoms, C_1-C_6 lower alkyl groups, or C_2-C_6 lower alkenyl groups;

R^3 represents a hydrogen atom, hydroxy group, cyano group, C_1-C_6 lower alkoxy group or C_2-C_7 lower alkanoyloxy group;

j represents an integer of 0-3;

k r presents 2 or 3;

R^4 is a group represented by :

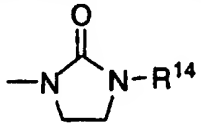
1) Formula: $-A^1-R^7$

(in the formula, R^7 represents a phenyl group which may be substituted by any number of the same or different {halogen atoms, hydroxy groups, amino groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyl groups, C_1-C_6 alkylsulfonyl groups, trifluoromethylsulfonyl groups, phenylsulfonyl groups {which may be substituted with a hydroxy group}, 1-pyrrolylsulfonyl groups, C_1-C_6 hydroxyalkyl sulfonyl groups, C_1-C_6 alkanoylamino groups, or a group represented by the formula: $-CONR^8R^9$} in which R^8 and R^9, identical to or different from each other, represent hydrogen atoms or C_1-C_6 lower alkyl groups; A^1 is a group represented by the formula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G represents G^1 or G^2; G^1 represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$; G^2 represents $-(C=NH)NH-SO_2-$, -CO-NH-NH-CO-, $-CO-NH-NH-CO-NR^{10}-$, $-CO-NH-CH_2-CO-$, $-CO-NH-NH-SO_2-$, or $-CO-N(CH_2-CO-OCH_3)-NH-CO-$; R^{10} represents a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; q represents 0 or 1);

2) Formula: $-A^2-R^{11}$

(wherein A^2 represents -CO- or $-SO_2-$; R^{11} represents:

a) A phenyl group which may be substituted by any number of the same or different {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



},

b) An aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, and optionally substituted with any of the same or different number of {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups}, or

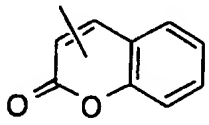
c) A group represented by the formula: $-CH_2-NR^{15}R^{16}$,

where R^{12}, R^{13}, R^{14} and R^{15}, identical or different groups, represent hydrogen atoms or C_1-C_6 lower alkyl gr ups and R^{16} represents (a phenyl group or a phenylalkyl group), which may be substituted by any number of the same or different halogen atoms, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group);

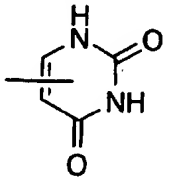
3) Formula: $-(CH_2)_n-R^{17}$

(in the formula, R^{17} is a group which may be substituted at any possible sites by any number of the same or different (halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, or C_1-C_6 lower alkoxy groups), representing

a hydrogen atom, cyano group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 hydroxyalkyl group, C_1-C_6 lower alkynyl group, C_3-C_6 cycloalkyl group, C_3-C_7 alkenoyl group, a group represented by the formula: $-(CHOH)CH_2OR^{18}$, a group represented by the formula: $-CO-NH-NH-CO-OR^{19}$, a group represented by the formula :



a group represented by the formula:



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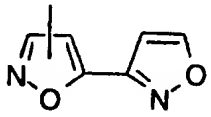

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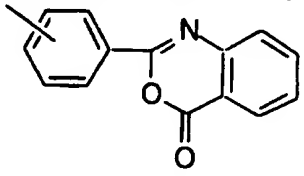

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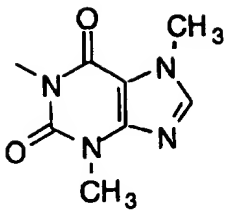

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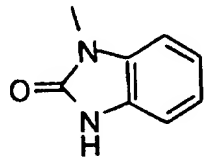

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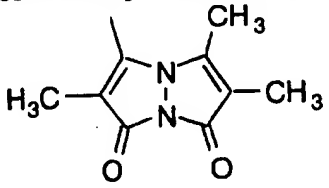

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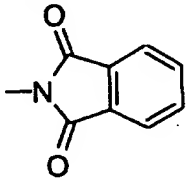

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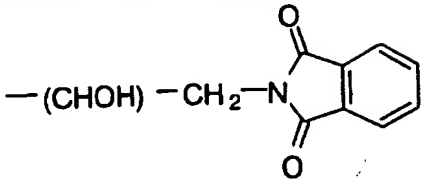
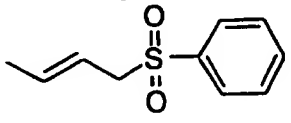
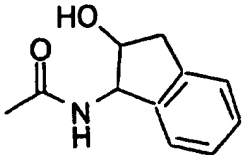


a group represented by the formula:



, or

a group represented by the formula:



in which n represents an integer of 1-4; R^{18} is C_1-C_6 lower alkyl group, C_2-C_6 lower alkenyl group, or C_2-C_6 lower alkynyl group and R^{19} represents a C_1-C_6 lower

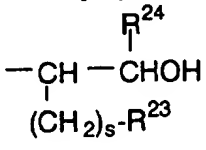
alkyl group);

4) Formula: $-(CH_2)_r-A^3-R^{20}$

(wherein r represents an integer of 0-3; A^3 represents a single bond, -CO-, -CO-NH-NH-CO-, -CO-NH-NH-CO-NH-, -CO-NH-CH_2-CO-, -CO-NH-NH-SO_2-, -(CHOH)-CH_2-, or -(CHOH)-CH_2OCH_2-; R^{20} represents an aromatic heterocyclic group containing 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms in which the aromatic heterocyclic group may be substituted by any number of the same or different (halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, or pyrrolyl groups) or may be condensed with a benzene ring to form a condensed ring); or

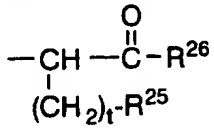
5) Formula: $-CH_2-CO-NR^{21}R^{22}$

(wherein R^{21} represents a hydrogen atom or C_1-C_6 lower alkyl group; R^{22} represents a hydrogen atom, C_1-C_6 lower alkyl group, a group represented by the formula:



;or

a group represented by the formula:



;

or R^{21} and R^{22} may be taken together with the nitrogen to form a 4 to 7-membered saturated heterocycles, which may contain an oxygen atom, sulfur atom, or another nitrogen atom; where s represents 0 or 1; t represents an integer of 0-2; R^{23} represents a hydrogen atom, hydroxy group, phenyl group, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group; R^{24} represents a hydrogen atom or phenyl group which may be substituted by hydroxy group; R^{25} represents a hydrogen atom, phenyl group (which may be substituted by hydroxy group), C_2-C_7 alkoxycarbonyl group, C_1-C_6 lower alkyl group, C_1-C_6 alkylthio group, or 3-indolyl group; and R^{26} represents a hydroxy group, amino group, C_1-C_6 lower alkoxy group, or phenylalkyloxy group);

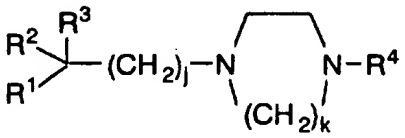
Excepting that if R^3 is a hydrogen atom, then, j is not 0, substituent for R^7 is not hydroxy, C_1-C_6 lower alkyl or C_1-C_6 lower alkoxy; G^1 is not -O- or -CO-; its substituents, if R^{11} is a phenyl group, are not C_1-C_6 lower alkyl group; R^{17} is not a hydrogen atom, C_2-C_7 alkoxycarbonyl group, or C_1-C_6 hydroxyalkyl group;

r is not 0 and A^3 is not a single bond or -CO-.

Furthermore, if R^3 represents a hydrogen atom and k represents 2, R^7 is not unsubstituted; m is not 0 and R^{11} is not a substituted or unsubstituted phenyl group.

If R^3 is a cyano group, R^7 is not unsubstituted, and the substituent groups for R^7 are not halogen atom, C_1-C_6 lower alkyl group or C_1-C_6 lower alkoxy group.]

The present invention provides a method of inhibiting the binding of chemokines to the receptor of a target cell and/or a method to inhibit its action onto a target cell using a pharmacological formulation containing as an active ingredient, a cyclic diamine derivative or its pharmacologically acceptable acid adduct (Invention 2) represented by the formula [II] below:



[II]

[wherein R^1 and R^2 are identical to or different from each other representing a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, in which the phenyl or aromatic heterocyclic group may be substituted by any number of halogen atoms, hydroxy groups, C_1-C_8 lower alkyl groups, C_1-C_6 lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, C_1-C_6 hydroxyalkyl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoylamino groups, dioxolanyl grpoups, or by group represented by the formula: $-NR^5R^6$, or else may be condensed with a benzene ring to form a condensed ring, furthermore above substituents for the phenyl or aromatic heterocyclic group and the condenced ring condenced with a benzene ring are optionally substituted by any ssubstituents independently selected from halogen atoms, hydroxy groups, or C_1-C_6 lower alkoxy groups, and R^5 and R^6 may be identical to or different from each other representing hydrogen atoms, C_1-C_6 lower alkyl groups, or C_2-C_6 lower alkenyl groups;

R^3 represents a hydrogen atom, hydroxy group, cyano group, C_1-C_6 lower alkoxy group or C_2-C_7 lower alkanoyloxy group;

j represents an integer of 0-3;

k represents 2 or 3 ;

R^4 is a group represented by :

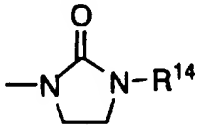
1) Formula: $-A^1-R^7$

(in the formula, R^7 represents a phenyl group which may be substituted by any number of the same or different {halogen atoms, hydroxy groups, amino groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyl groups, C_1-C_6 alkylsulfonyl groups, trifluoromethylsulfonyl groups, phenylsulfonyl groups {which may be substituted with a hydroxy group}, 1-pyrrolylsulfonyl groups, C_1-C_6 hydroxyalkylsulfonyl groups, C_1-C_6 alkanoylamino groups, or a group represented by the formula: $-CONR^8R^9$} in which R^8 and R^9, identical to or different from each other, represent hydrogen atoms or C_1-C_6 lower alkyl groups; A^1 is a group represented by the formula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G represents G^1 or G^2; G^1 represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$; G^2 represents $-(C=NH)NH-SO_2-$, -CO-NH-NH-CO-, $-CO-NH-NH-CO-NR^{10}-$, $-CO-NH-CH_2-CO-$, $-CO-NH-NH-SO_2-$, or $-CO-N(CH_2-CO-OCH_3)-NH-CO-$; R^{10} represents a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; q represents 0 or 1);

2) Formula: $-A^2-R^{11}$

(wherein A^2 represents -CO- or $-SO_2-$; R^{11} represents:

a) A phenyl group which may be substituted by any number of the same or different {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



),

b) An aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, and optionally substituted with any of the same or different number of {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups}, or

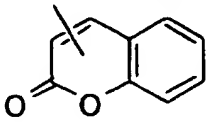
c) A group represented by the formula: $-CH_2-NR^{15}R^{16}$,

where R^{12}, R^{13}, R^{14} and R^{15}, identical or different groups, represent hydrogen atoms or C_1-C_6 lower alkyl groups and R^{16} represents {a phenyl group or a phenylalkyl group}, which may be substituted by any number of the same or different halogen atoms, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group);

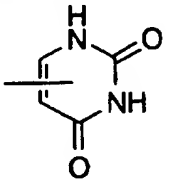
3) Formula: $-(CH_2)_n-R^{17}$

(in the formula, R^{17} is a group which may be substituted at any possible sites by any number of the same or different {halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, or C_1-C_6 lower alkoxy groups), representing

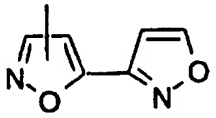
a hydrogen atom, cyano group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 hydroxyalkyl group, C_1-C_6 lower alkynyl group, C_3-C_6 cycloalkyl group, C_3-C_7 alkenoyl group, a group represented by the formula: $-(CHOH)CH_2OR^{18}$, a group represented by the formula: $-CO-NH-NH-CO-OR^{19}$, a group represented by the formula :



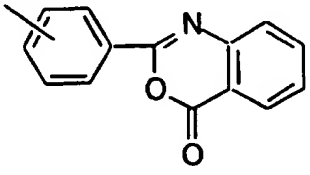
a group represented by the formula:



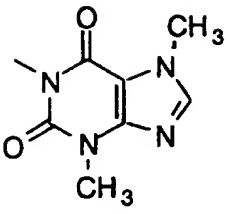
a group represented by the formula:



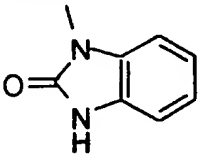
a group represented by the formula:



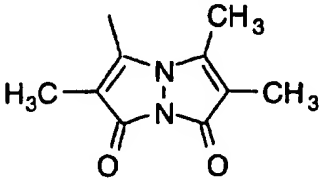
a group represented by the formula :



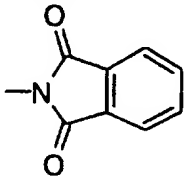
a group represented by the formula:



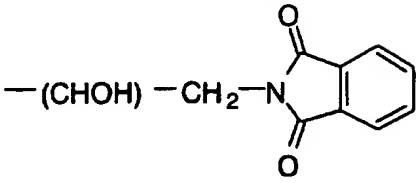
a group represented by the formula:



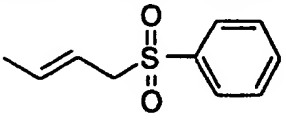
a group represented by the formula:



a group represented by the formula:

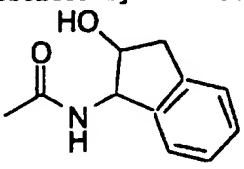


a group represented by the formula:



, or

a group represented by the formula:



in which n represents an integer of 1-4; R^{18} is C_1-C_6 lower alkyl group, C_2-C_6 lower alkenyl group, or C_2-C_6 lower alkynyl group and R^{19} represents a C_1-C_6 lower

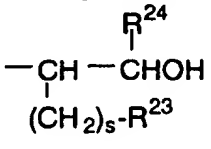
alkyl group);

4) Formula: $-(CH_2)_r-A^3-R^{20}$

(wherein r represents an integer of 0-3; A^3 represents a single bond, -CO-, -CO-NH-NH-CO-, -CO-NH-NH-CO-NH-, -CO-NH-CH_2-CO-, -CO-NH-NH-SO_2-, -(CHOH)-CH_2-, or -(CHOH)-CH_2OCH_2-; R^{20} represents an aromatic heterocyclic group containing 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms in which the aromatic heterocyclic group may be substituted by any number of the same or different {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, or pyrrolyl groups} or may be condensed with a benzene ring to form a condensed ring);

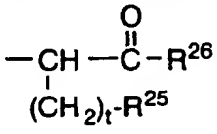
5) Formula: $-CH_2-CO-NR^{21}R^{22}$

(wherein R^{21} represents a hydrogen atom or C_1-C_6 lower alkyl group; R^{22} represents a hydrogen atom, C_1-C_6 lower alkyl group, a group represented by the formula:



;or

a group represented by the formula:



;

or R^{21} and R^{22} may be taken together with the nitrogen to form a 4 to 7-membered saturated heterocycles, which may contain an oxygen atom, sulfur atom, or another nitrogen atom; where s represents 0 or 1; t represents an integer of 0-2; R^{23} represents a hydrogen atom, hydroxy group, phenyl group, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group; R^{24} represents a hydrogen atom or phenyl group which may be substituted by hydroxy group; R^{25} represents a hydrogen atom, phenyl group {which may be substituted by hydroxy group}, C_2-C_7 alkoxycarbonyl group, C_1-C_6 lower alkyl group, C_1-C_6 alkylthio group, or 3-indolyl group; and R^{26} represents a hydroxy group, amino group, C_1-C_6 lower alkoxy group, or phenylalkyloxy group);

6) A hydrogen atom, C_1-C_6 alkanoyl group, or C_2-C_7 alkoxycarbonyl group.]

Here, the compounds represented by the above formula [II] have activities to inhibit the binding of chemokines such as MIP-1α and/or MCP-1 and the like

to the receptor of a target cell and activities to inhibit physiological activities of cells caused by chemokines such as MIP-1α and/ r MCP-1 and the like.

Preferred Embodiments of the Invention

(1) On Invention 1

In the above formula [I], R^1 and R^2 are identical to or different from each other representing a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, in which the phenyl or aromatic heterocyclic group may be substituted by any number of halogen atoms, hydroxy groups, C_1-C_8 lower alkyl groups, C_1-C_6 lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, C_1-C_6 hydroxyalkyl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups, C_1-C_6 alkanoylamino groups, dioxolanyl grpoups, or by group represented by the formula: $-NR^5R^6$, or else may be condensed with a benzene ring to form a condensed ring. Unsubstituted aromatic heterocyclic groups having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms are specifically, for example, thienyl, furyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazinyl, triazolyl, oxadiazolyl, thiadiazolyl group and the like, preferably including thienyl, furyl, pyrrolyl, and pyridyl groups.

The halogen atom as substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2 include fluorine atoms, chlorine atoms, bromine atoms, iodine atoms, suitably including fluorine atoms and chlorine atoms. The C_1-C_8 lower alkyl groups mean C_1-C_8 straight-chain or branched alkyl groups such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl, 2-methylpentyl, 1-ethylbutyl, and the like, suitably specifically including, methyl, ethyl, and isopropyl groups. The C_1-C_6 lower alkoxy groups mean groups consisting of C_1-C_6 part of the aforementioned C_1-C_8 lower alkyl groups and oxy groups, specifically, for example, methoxy group and ethoxy group. The C_1-C_6 hydroxyalkyl groups are groups in which C_1-C_6 part of the aforementioned C_1-C_8 l wer alkyl groups are substituted at their any p sitions by a hydroxy group, preferably and specifically for example, hydroxymethyl group, 2-hydroxyethyl

group, and the like. The C_2-C_7 alkoxycarbonyl groups mean the af rementioned C_1-C_6 lower alkoxy groups and carbonyl groups, preferably specifically for example, a methoxycarbonyl group and ethoxycarbonyl group. The C_2-C_7 lower alkanoylamino groups mean C_2-C_7 lower straight-chain or branched alkanoylamino groups such as acetylamino, propanoylamino, butanoylamino, pentanoylamino, hexanoylamino, heptanoylamino, isobutyrylamino, 3-methylbutanoylamino, 2-methylbutanoylamino, pivaloylamino, 4-methylpentanoylamino, 3,3-dimethylbutanoylamino, 5-methylhexanoylamino group, and the like, where the preferred and specific example includes an acetylamino group. Condensed rings obtained by condensation with a benzene ring mean a ring obtained by the condensation with a benzene ring of a phenyl group or an aromatic monocyclic heterocyclic ring having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, at any possible sites, suitably and specifically for example, naphthyl, indolyl, benzofuranyl, benzothienyl, quinolyl group, indolyl group, benzimidazolyl group.

R^5 and R^6 represent each independently hydrogen atoms, C_1-C_6 lower alkyl groups, or C_2-C_6 lower alkenyl groups. The C_1-C_6 lower alkyl groups are the same as defined for the aforementioned C_1-C_6 part of the C_1-C_8 lower alkyl groups as substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given for the preferred specific examples. The C_2-C_6 lower alkenyl groups are for example, C_2-C_6 straight-chain or branched alkenyl groups such as vinyl, allyl, 2-butenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 4-methyl-3-pentenyl, and the like, where preferred specific examples include allyl, 2-butenyl, and 3-butenyl group.

Furthermore above substituents for the phenyl or aromatic heterocyclic group and the condenced ring condenced with a benzene ring in R^1 and R^2 are optionally substituted by any ssubstituents independently selected from halogen atoms, hydroxy groups, or C_1-C_6 lower alkoxy groups. The halogen atoms and C_1-C_6 lower alkoxy groups are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, and the same examples can be listed as preferred specific examples .

R^3 in the above formula [I] represents a hydrogen atom, hydroxy group, cyan group, C_1-C_6 lower alkoxy group, or C_2-C_7 lower alkanoyloxy group. Th C_1-C_6 lower alkoxy groups are th same as defined for the C_1-C_6 lower alkoxy groups

in the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given for their preferred specific examples. The C_2-C_7 lower alkanoyloxy groups mean C_2-C_7 lower straight-chain or branched alkanoyloxy groups such as acetyloxy, propanoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, isobutyryloxy, 3-methylbutanoyloxy, 2-methylbutanoyloxy, pivaloyloxy, 4-methylpentanoyloxy, 3,3-dimethylbutanoyloxy, 5-methylhexanoyloxy group, and the like, where the preferred and specific example includes an acetyloxy group. Preferred specific examples for R^3 include a hydrogen atom and hydroxy group.

In the above formula [I], j represents an integer of 0-3. If R^3 represents a hydrogen atom, j is not 0. It is particularly preferred for j to be 2.

k in the above formula [I] represents 2 or 3; it is particularly preferred to use a homopiperazine derivative in which k is 3.

R^4 in the above formula [I] represents a group represented by:

1) Formula: $-A^1-R^7$,
2) Formula: $-A^2-R^{11}$,
3) Formula: $-(CH_2)_n-R^{17}$,
4) Formula: $-(CH_2)_r-A^3-R^{20}$, or
5) Formula: $-(CH_2)-CO-NR^{21}R^{22}$.

Here -CO- represents a carbonyl group. It is particularly preferred for R^4 to be represented by formula 1): $-A^1-R^7$ or formula 4): $-(CH_2)_r-A^3-R^{20}$.

R^7 represents a phenyl group which may be substituted by any number of the same or different (halogen atoms, hydroxy groups, amino groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyl groups, C_1-C_6 alkylsulfonyl groups, trifluoromethylsulfonyl groups, phenylsulfonyl groups (which may be substituted with a hydroxy group), 1-pyrrolylsulfonyl groups, C_1-C_6 hydroxyalkyl sulfonyl groups, C_1-C_6 alkanoylamino groups, or a group represented by the formula: $-CONR^8R^9$). However, if R^3 represents a hydrogen atom, the substituent for a phenyl in R^7 is not a hydroxy, C_1-C_6 lower alkyl, or C_1-C_6 lower alkoxy; if R^3 is a hydr gen at m and k=2, R^7 is not an unsubstituted phenyl group;

if R^3 represents a cyano group, R^7 is not unsubstituted and the substitu nt for a phenyl in R^7 is not a hal gen atom, C_1-C_6 lower alkyl, or C_1-C_6 lower alkoxy group.

The halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, C_2-C_7 alkoxycarbonyl groups, and C_2-C_7 alkanoylamino groups as substituents for a phenyl in R^7 are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, and the same examples can be listed as preferred specific examples. The C_2-C_7 lower alkanoyl groups mean C_2-C_7 lower straight-chain or branched alkanoyl groups such as acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl, isobutyryl, 3-methylbutanoyl, 2-methylbutanoyl, pivaloyl, 4-methylpentanoyl, 3,3-dimethylbutanoyl, 5-methylhexanoyl group, and the like, where the preferred and specific example includes an acetyl group. The C_1-C_6 alkylsulfonyl groups mean those consisting of the aforementioned C_1-C_6 part of the C_1-C_8 lower alkyl groups and sulfonyl groups, preferably and specifically, for example, a methylsulfonyl group. The phenylsulfonyl groups may be substituted with a hydroxy group at any position. The C_1-C_6 hydroxyalkylsulfonyl groups mean those consisting of the aforementioned C_1-C_6 hydroxyalkyl groups and sulfonyl groups, preferably and specifically, for example, a (2-hydroxyethyl) sulfonyl group. R^8 and R^9, the same or different groups, represent hydrogen atoms or C_1-C_6 lower alkyl groups. The C_1-C_6 lower alkyl groups as R^8 and R^9 are the same as defined for the aforementioned C_1-C_6 part of the C_1-C_8 lower alkyl groups as substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, and the same examples are listed for their preferred specific examples.

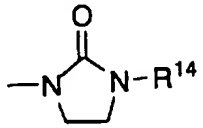
A^1 is a group represented by the formula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G represents G^1 or G^2; G^1 represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$; G^2 represents $-(C=NH)NH-SO_2-$, -CO-NH-NH-CO-, $-CO-NH-NH-CO-NR^{10}-$, $-CO-NH-CH_2-CO-$, $-CO-NH-NH-SO_2-$, or $-CO-N(CH_2-CO-OCH_3)-NH-CO-$; R^{10} represents a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; q represents 0 or 1); however, if R^3 is a hydrogen atom, G^1 is not -O- or -CO-; if R^3 represents a hydrogen atom and if k=2, m is not 0. In the above formula, -CO- means a carbonyl group and $-SO_2-$ means a sulfonyl group. Preferred A^1 groups are specifically, for example, those represented by the formula $-(CH_2)_m-$, with m being preferably 1. Preferred A^1 groups are also specifically, for example, $-(CH_2)_p-CO-NH-NH-CO-$

$(CH_2)_q$-, $-(CH_2)_p$-CO-NH-NH-CO-NH-$(CH_2)_q$-, $-(CH_2)_p$-CO-NH-CH_2-CO-$(CH_2)_q$-: with p being preferably 1.

A^2 represents -CO- (carbonyl group) or $-SO_2$- (sulfonyl group).

R^{11} represents:

a) A phenyl group which may be substituted by any number of the same or different {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



},

b) An aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, and optionally substituted with any of the same or different number of {halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups}, or

c) A group represented by the formula: $-CH_2-NR^{15}R^{16}$.

However if R^3 represents a hydrogen atom, the substituent group for a phenyl group in R^{11} is not a C_1-C_6 lower alkoxy group; if R^3 represents a hydrogen atom and k is 2, R^{11} is not a substituted or unsubstituted phenyl group. The halogen atoms, C_1-C_6 lower alkyl groups, or C_1-C_6 lower alkoxy groups as substituents for the groups in R^{11} are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, and the same examples can be given as preferred specific examples.

Specific examples for R^{11} in which the aromatic monocyclic heterocyclic group is unsubstituted can be the same specific examples for the aromatic heterocyclic groups with no substituents in R^1 and R^2. Preferred examples specifically include a pyridyl group.

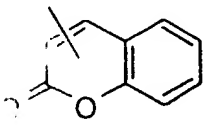
R^{12}, R^{13}, R^{14} and R^{15} represent each independently hydrogen atoms or C_1-C_6 lower alkyl groups. The C_1-C_6 lower alkyl groups are of the same definition for the aforementioned C_1-C_6 part of th C_1-C_6 lower alkyl groups as substituents

anyl group or an aromatic heterocyclic gr up in R^1 and R^2, where the same can be listed as preferred specific examples.

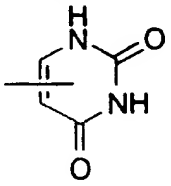
R^{16} represents a {phenyl group or phenylalkyl group} which may be ited by any number of the same or different {halogen atoms, C_1-C_6 lower oups, or C_1-C_6 lower alkoxy group}. The halogen atom, C_1-C_6 lower alkyl . C_1-C_6 lower alkoxy group as substituents are the same as defined for -mentioned substituents for a phenyl group or an aromatic heterocyclic R^1 and R^2, where the same examples can be given as preferred specific s. The phenylalkyl group means a group consisting of a phenyl group and lkylene group, preferably and specifically for example, a benzyl group.

' is a group which may be substituted at any possible sites by any number ame or different {halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, koxy group s}, representing

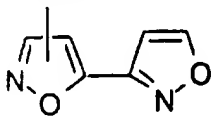
en atom, cyano group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 hydroxyalkyl group, alkynyl group, C_3-C_6 cycloalkyl group, C_2-C_7 alkenoyl group, a group y the formula: $-(CHOH)CH_2OR^{18}$, a group represented by the formula: ^{19}, a group represented by the formula :



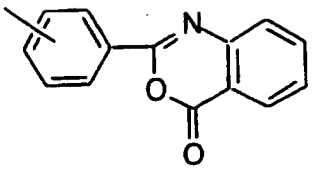
epresented by the formula:



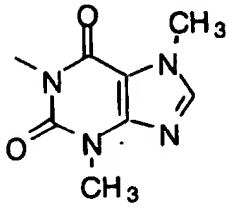
ented by the formula:



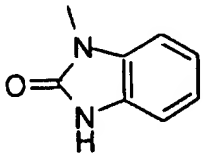
represented by the formula:



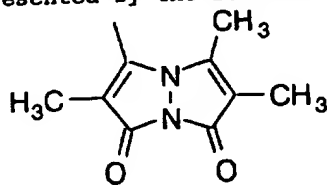
a group represented by the formula :



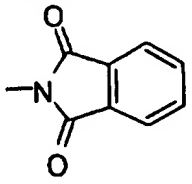
a group represented by the formula:



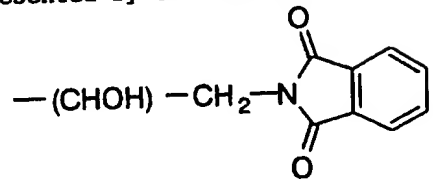
a group represented by the formula:



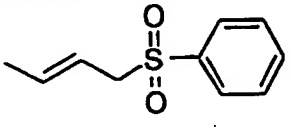
a group represented by the formula:



a group represented by the formula:

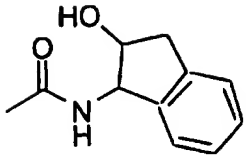


a group represented by the formula:



, or

a group represented by the formula:



If, however, R^3 represents a hydrogen atom, R^{17} is not a hydrogen atom, C_2-C_7 alkoxycarbonyl group, or C_1-C_6 hydroxyalkyl group. R^{17} may be bonded at any possible site to an alkylene group $-(CH_2)_n-$. The C_2-C_7 alkoxycarbonyl and C_1-C_6 hydroxyalkyl groups are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples may be given as preferred specific examples. The C_1-C_6 lower alkynyl group means a C_2-C_6 straight-chain or branched alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 2-butynyl, 3-butynyl, 4-pentynyl, 5-hexynyl, 1-methyl-4-pentynyl group, and the like, preferably and specifically, for example, ethynyl group and 1-propynyl group. The C_3-C_6 cycloalkyl groups mean cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl groups and the like. The C_3-C_7 lower alkenoyl group means a C_3-C_7 straight-chain or branched alkenoyl groups such as propenoyl, 2-metylpropenoyl, 2-buenoyl, 3-butenoyl, 2-methyl-3-butenoyl, 3-methyl-2-butenoyl, 2-pentenoyl, 4-pentenoyl, 2-methyl-2-pentenoyl, 2,2-dimethyl-4-pentenoyl, 2-hexenoyl, 3-hexenoyl, 6-heptenoyl, and the like, preferably and specifically, for example propenoyl and 2-metylpropenoyl group.

The halogen atom, C_1-C_6 lower alkyl group or C_1-C_6 lower alkoxy groups as substituents for R^{17} are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, and the same examples can be given as preferred specific examples.

R^{18} represents a C_1-C_6 lower alkyl group, C_2-C_6 lower alkenyl group, or C_2-C_6 lower alkynyl group. The C_1-C_6 lower alkyl groups are the same as defined for the aforementioned C_1-C_6 part of the C_1-C_6 lower alkyl groups as substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given as preferred specific examples. The C_2-C_6 lower alkenyl groups are the same as the C_2-C_6 lower alkenyl groups in the aforementioned R^5 and R^6, where the preferred examples are specifically allyl, 2-butenyl, and 3-butenyl group. The C_2-C_6 lower alkynyl groups are the same as the C_2-C_6 lower alkynyl groups in the aforementioned R^{17} where the pref rred examples are specifically 2-prop ynyl group and 3-butynyl group.

R^{19} represents a C_1-C_6 lower alkyl group. Here, the C_1-C_6 lower alkyl group is the same as defined for the aforementioned C_1-C_6 part of the C_1-C_8 lower alkyl groups as substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given as preferred specific examples.

n is an integer of 1-4. It is particularly preferred for the n to be 1 or 2.

A^3 represents a single bond, -CO-, -CO-NH-NH-CO-, -CO-NH-NH-CO-NH-, -CO-NH-CH_2-CO-, -CO-NH-NH-SO_2-, -(CHOH)-CH_2-, or -(CHOH)-CH_2OCH_2-. However, if R^3 represents a hydrogen atom, A^3 is not a single bond. Here, -CO- means a carbonyl group and -SO_2- means a sulfonyl group. A^3 is preferably a single bond or -CO-NH-NH-CO-.

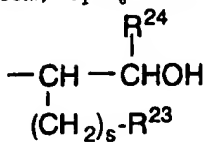
R^{20} represents an aromatic heterocyclic group containing 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms in which the aromatic heterocyclic group may be substituted by any number of the same or different (halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, or pyrrolyl groups) or may be condensed with a benzene ring to form a condensed ring. As to specific examples in which the aromatic monocyclic heterocyclic group R^{20} has no substitution, the same specific example can be given as in the cases with no substituents on the aromatic heterocyclic rings in R^1 and R^2; preferred examples are spec ifically a pyridyl group and is oxazolyl group.

The halogen atom, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group as substituents for the aromatic heterocyclic group in R^{20} are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given as suitable specific examples. The condensed ring obtained by condensation with a benzene ring in R^{20} is the same as defined for the condenced ring in R^1 and R^2, where the same examples can be given as suitable specific examples.

r is an integer of 0-3. However, if R^3 represents a hydrogen atom, r is not 0. In particular, it is preferred for r to be 1.

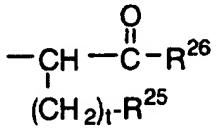
R^{21} represents a hydrogen atom or C_1-C_6 lower alkyl group, R^{22} represents

a hydrogen atom, C_1-C_6 lower alkyl group, a group represented by the formula:



;or

a group represented by the formula:



;

or may be taken together with the nitrogen to form a 4 to 7-membered saturated heterocycles, which may contain an oxygen atom, sulfur atom, or another nitrogen atom. The C_1-C_6 lower alkyl groups in R^{21} and R^{22} are the same as defined for the aforementioned C_1-C_6 part of the C_1-C_6 lower alkyl groups as substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given for the preferred specific examples. Saturated heterocyclic rings consisting of R^{21} ,R^{22}, and the nitrogen include azetidine, pyrrolidine, piperidine, perhydroazepine, morpholine, thiamorpholine, piperazine, homopiperazine, and the like; preferred specific examples include piperidine, morpholine, and thiamorpholine.

s represents 0 or 1 and t represents an integer of 0-2.

R^{23} represents a hydrogen atom, hydroxy group, phenyl group, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group. The C_1-C_6 lower alkyl group and C_1-C_6 lower alkoxy groups as R^{23} are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given for the preferred specific examples .

R^{24} represents a hydrogen atom or phenyl group, where the phenyl group may be substituted by hydroxy group at any position.

R^{25} represents a hydrogen atom, phenyl group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 lower alkyl group, C_1-C_6 alkylthio group, or 3-indolyl group, where the phenyl group may be substituted by hydroxy group at any position. The C_2-C_7 alkoxycarbonyl group and C_1-C_6 lower alkyl group as R^{25} are the same as defined for the aforementioned substituents for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given for the

preferred specific examples. The C_1-C_6 alkylthio group as R^{25} means a group consisting of thio group and C_1-C_6 part of the aforementioned C_1-C_8 lower alkyl groups for substituent in R^1 and R^2, specifically, for example, methylthio group and ethylthio group.

R^{26} represents a hydroxy group, amino group, C_1-C_6 lower alkoxy group, or phenylalkyloxy group. The C_1-C_6 lower alkoxy group is the same as defined for the aforementioned C_1-C_6 lower alkoxy group as substituent for a phenyl group or an aromatic heterocyclic group in R^1 and R^2, where the same examples can be given for the preferred specific examples. The phenylalkyl group means a group consisting of a phenyl group, a C_1-C_6 alkylene group, and a oxy group, preferably and specifically for example, a benzyl oxy group.

(2) On Invention 2

R^1, R^2, R^3, j, and k in the above formula [II] are as the same as defined in the respective terms for the above formula [I] and the same examples can be listed for their preferred specific examples. R^4 in the above formula [II] includes R^4 defined in the respective terms for the above formula [I], where the same examples can be listed for their preferred specific examples, and furthermore R^4 in the above formula [II] represents a hydrogen atom, C_1-C_6 alkanoyl group, or C_2-C_7 alkoxycarbonyl group. However, the above formula [II] does not involve the same limitations as made in the above formula [I] with respect to cases where R^3 represents a hydrogen atom, where R^3 represents a hydrogen atom and k represents 2, and where R^3 represents cyano group.

The cyclic diamine derivative represented by the formula [II] above or its pharmacologically acceptable acid adduct can be used to prepare a chemokine receptor antagonist preparation of the present invention by formulating the therapeutically required amount and a carrier and/or diluent into a pharmaceutical composition. Thus, the cyclic diamine derivative shown by the above formula [II] or its pharmacologically acceptable acid adduct can be administered orally or by parenterally, for example, intravenously, subcutaneously, intramuscularly, percutaneously or intrarectally.

The oral administration can be acc mplished in the form of tablets, pills, granules, powder, solution, suspension, capsules, etc.

The tablets for example can be prepared using a vehicle such as lact se, starch and crystallized cellulose; binder such as carboxymethylcellulos , methylcellulose, and polyvinylpyrrolidone; disintegrator such as sodium alginate, sodium bicarbonate and sodium lauryl sulfate, etc.

Pills, powder and granule preparations can be prepared by a standard method using the vehicles mentioned above. Solution or suspension can be prepared by a standard method using glycerin ester such as tricaprylin and triacetin or alcohols such as ethanol. Capsules can be made by charging granules, powder or solution in gelatin, etc.

Subcutaneous, intramuscular or intravenous preparations can be prepared as an injection using aqueous or nonaqueous solution. Aqueous solution for example may include isotonic sodium chloride solution. Nonaqueous solutions may include for example, propyleneglycol, polyethyleneglycol, olive oil, ethyl oleate, etc., and optionally, one can add antiseptics and stabilizers. For injection, one can be sterilized by filtration through a bacterial filter or combination of disinfectant .

Percutaneous administration may be in the form of an ointment or cream, and ointment can be prepared in the standard manner using fatty oils such as castor oil and olive oil, or Vaseline, while creams can be made using fatty oils or emulsifying agent such as diethyleneglycol and sorbitan esters of fatty acid.

For intrarectal administration, one can use standard suppositories using gelatin soft capsules , etc.

The cyclic diamine derivative of the present invention or its pharmacologically acceptable acid adduct is administered at a dose that varies depending on the type of disease, route of administration, age and sex of patient, and severity of disease, but is likely to be 1-500 mg/day in an average adult.

(3) Matter common throughout Invention 1 and Invention 2

Preferred specific examples for the cyclic diamine derivatives in the

above formula [I] r formula [II] include comp unds having each substituent as shown in the following Tables 1.1 - 1.25.

Table 1.1 ~ Table 1.25

Tabl 1.1

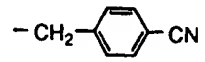
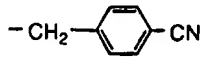
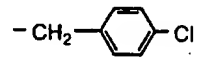
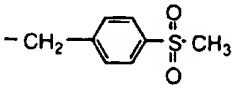
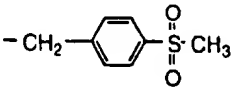
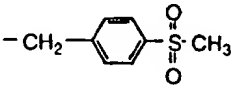
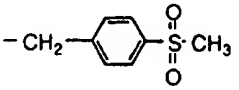
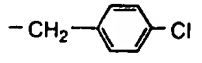
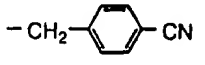
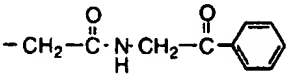
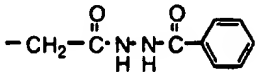
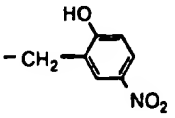
Compound No.	R^1	R^2	R^3	j	k	R^4
1			CN	2	2	
2			CN	2	3	
3			CN	2	3	
4			CN	2	3	
5			H	0	3	
6			H	1	3	
7			H	2	2	
8			H	2	2	
9			H	2	2	
10			H	2	2	
11			H	2	2	
12			H	2	2	

Table 1.2

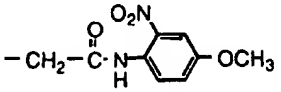
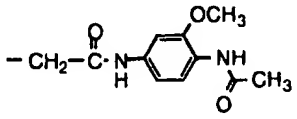
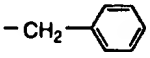
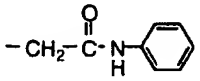
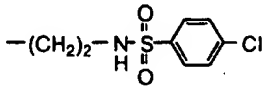
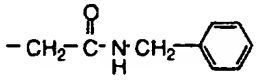
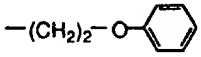
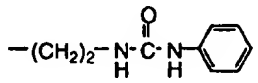
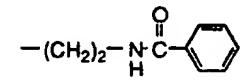
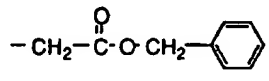
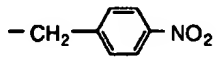
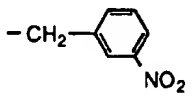
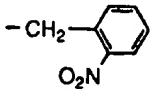
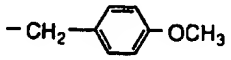
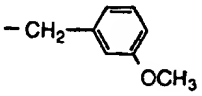
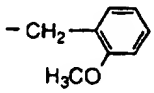
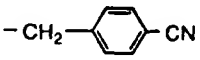
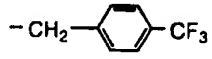
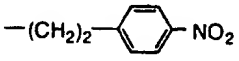
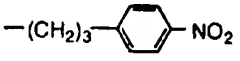
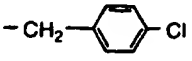
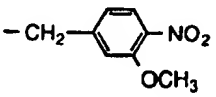
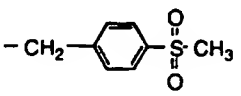
Compound No.	R^1	R^2	R^3	j	k	R^4
13			H	2	2	
14			H	2	2	
15			H	2	3	
16			H	2	3	
17			H	2	3	
18			H	2	3	
19			H	2	3	
20			H	2	3	
21			H	2	3	
22			H	2	3	
23			H	2	3	
24			H	2	3	

Table 1.3

Compound No.	R^1	R^2	R^3	j	k	R^4
25			H	2	3	
26			H	2	3	
27			H	2	3	
28			H	2	3	
29			H	2	3	
30			H	2	3	
31			H	2	3	
32			H	2	3	
33			H	2	3	
34			H	2	3	
35			H	2	3	
36			H	2	3	

Tabl 1.4

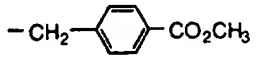
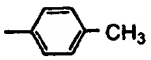
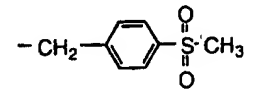
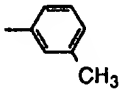
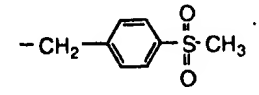
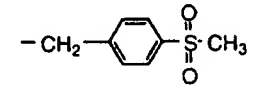
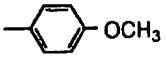
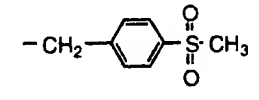
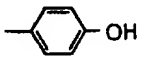
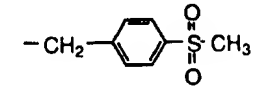
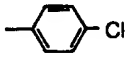
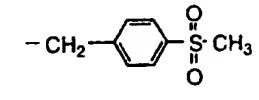
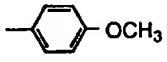
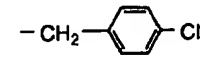
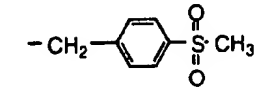
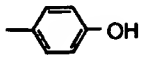
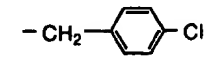
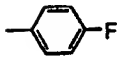
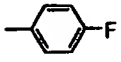
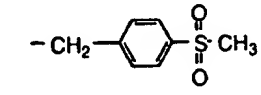
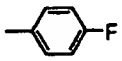
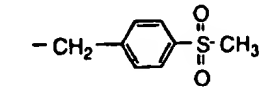
Compound No.	R^1	R^2	R^3	j	k	R^4
37			H	2	3	
38			H	2	3	
39			H	2	3	
40			H	2	3	
41			H	2	3	
42			H	2	3	
43			H	2	3	
44			H	2	3	
45			H	2	3	
46			H	2	3	
47			H	2	3	
48			H	2	3	

Table 1.5

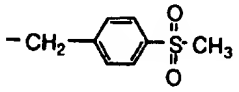
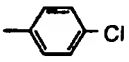
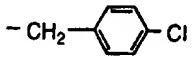
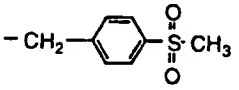
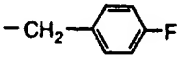
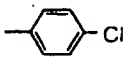
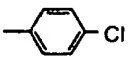
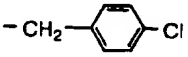
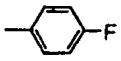
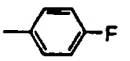
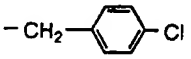
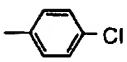
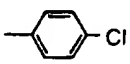
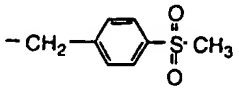
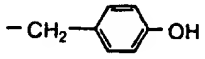
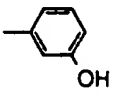
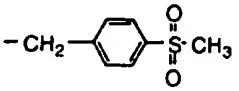
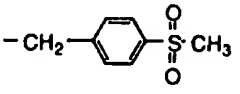
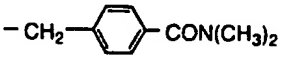
Compound No.	R^1	R^2	R^3	j	k	R^4
49			H	2	3	
50			H	2	3	
51			H	2	3	
52			H	2	3	
53			H	2	3	
54			H	2	3	
55			H	2	3	
56			H	2	3	
57			H	2	3	
58			H	2	3	
59			H	2	3	
60			H	2	3	

Table 1.6

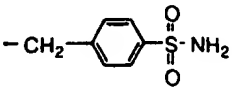
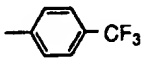
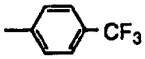
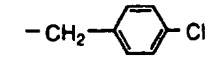
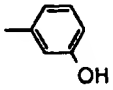
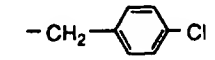
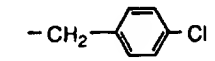
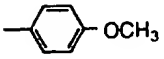
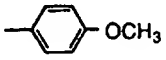
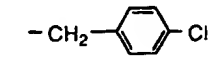
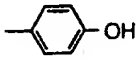
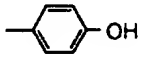
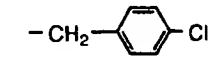
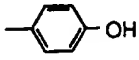
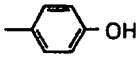
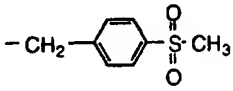
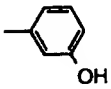
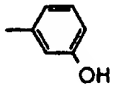
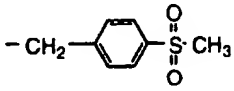
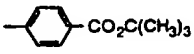
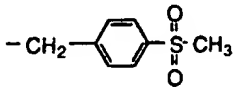
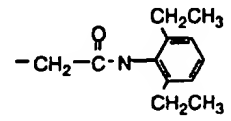
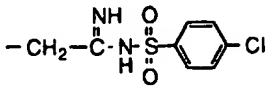
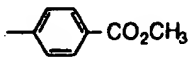
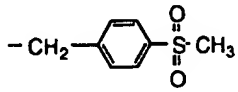
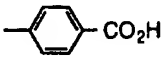
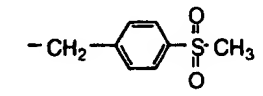
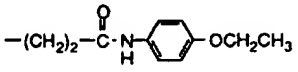
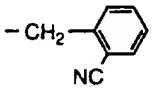
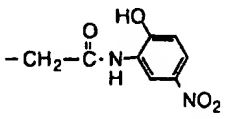
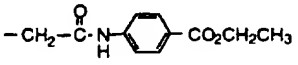
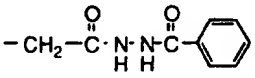
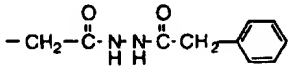
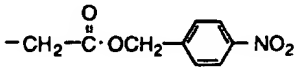
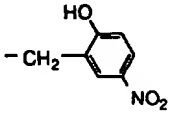
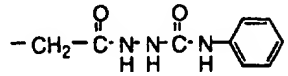
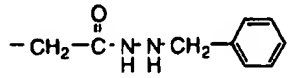
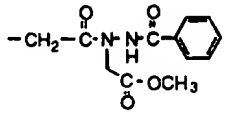
Compound No.	R^1	R^2	R^3	j	k	R^4
61			H	2	3	
62			H	2	3	
63			H	2	3	
64			H	2	3	
65			H	2	3	
66			H	2	3	
67			H	2	3	
68			H	2	3	
69			H	2	3	
70			H	2	3	
71			H	2	3	
72			H	2	3	

Table 1.7

Compound No.	R^1	R^2	R^3	j	k	R^4
73			H	2	3	
74			H	2	3	
75			H	2	3	
76			H	2	3	
77			H	2	3	
78			H	2	3	
79			H	2	3	
80			H	2	3	
81			H	2	3	
82			H	2	3	
83			H	2	3	
84			H	2	3	

Tabl 1.8

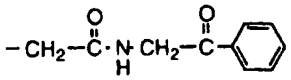
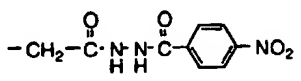
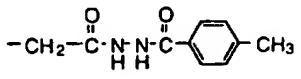
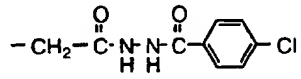
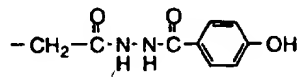
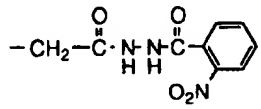
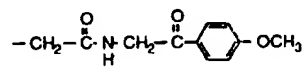
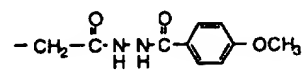
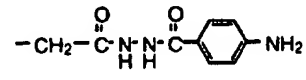
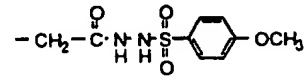
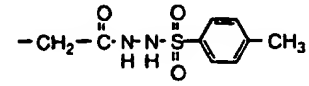
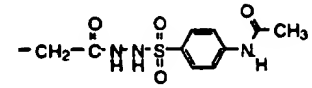
Compound No.	R^1	R^2	R^3	j	k	R^4
85			H	2	3	
86			H	2	3	
87			H	2	3	
88			H	2	3	
89			H	2	3	
90			H	2	3	
91			H	2	3	
92			H	2	3	
93			H	2	3	
94			H	2	3	
95			H	2	3	
96			H	2	3	

Table 1.9

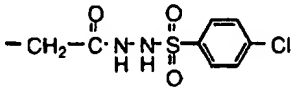
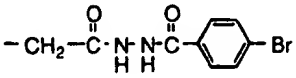
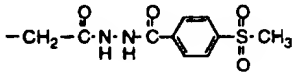
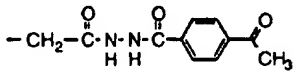
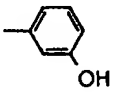
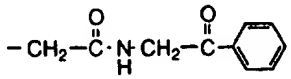
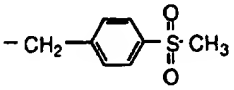
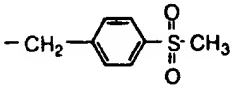
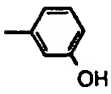
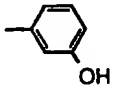
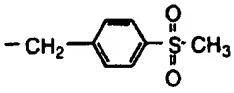
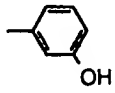
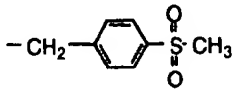
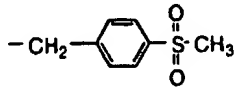
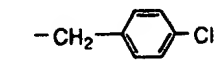
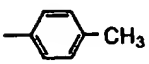
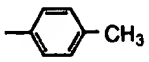
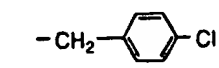
Compound No.	R^1	R^2	R^3	j	k	R^4
97			H	2	3	
98			H	2	3	
99			H	2	3	
100			H	2	3	
101			H	2	3	
102			H	3	3	
103			OCH_3	2	3	
104			OCH3	2	3	
105			$OCOCH_3$	2	3	
106			OH	2	3	
107			OH	2	3	
108			OH	2	3	

Table 1.10

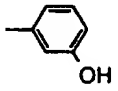
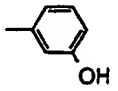
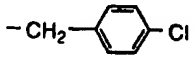
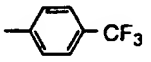
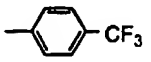
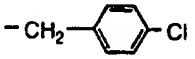
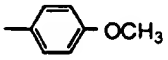
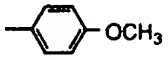
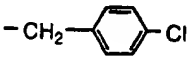
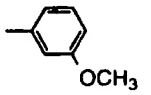
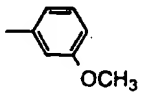
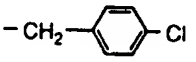
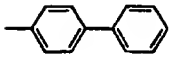
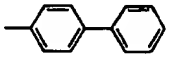
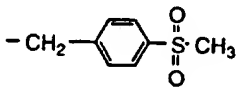
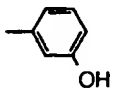
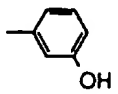
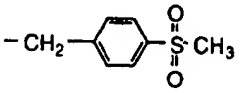
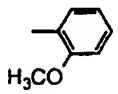
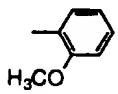
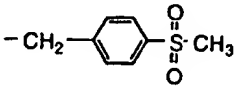
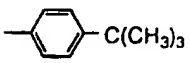
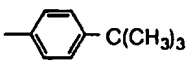
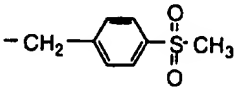
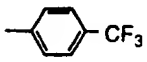
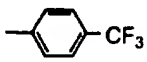
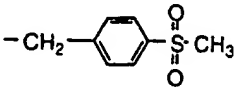
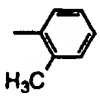
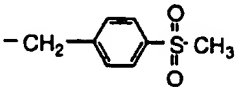
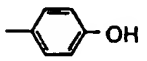
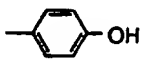
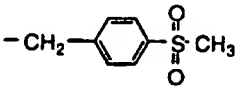
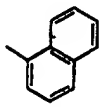
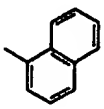
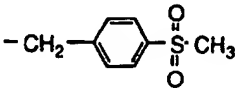
Compound No.	R^1	R^2	R^3	j	k	R^4
109			OH	2	3	
110			OH	2	3	
111			OH	2	3	
112			OH	2	3	
113			OH	2	3	
114			OH	2	3	
115			OH	2	3	
116			OH	2	3	
117			OH	2	3	
118			OH	2	3	
119			OH	2	3	
120			OH	2	3	

Table 1.11

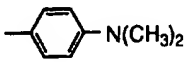
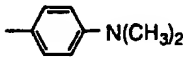
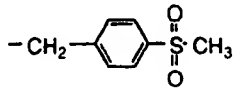
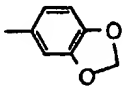
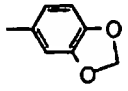
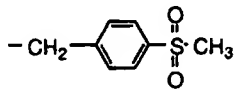
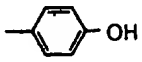
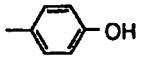
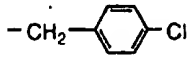
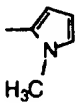
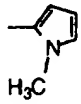
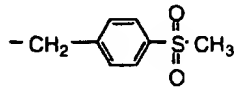
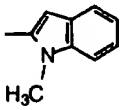
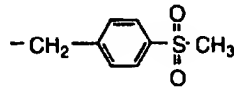
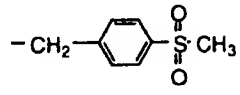
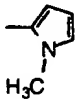
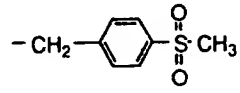
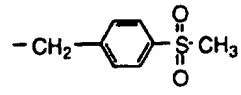
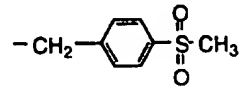
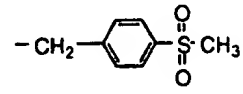
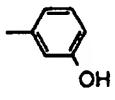
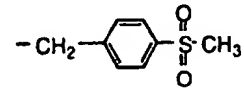
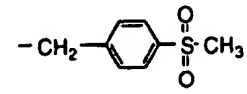
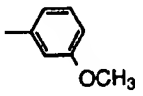
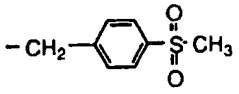
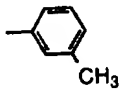
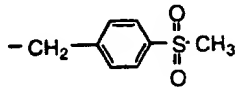
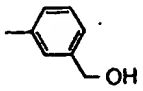
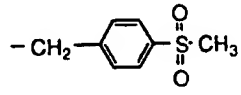
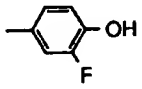
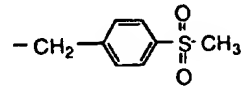
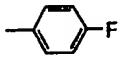
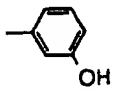
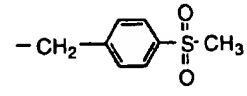
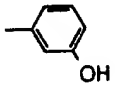
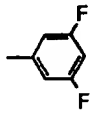
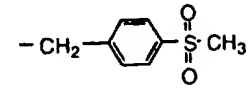
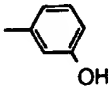
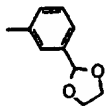
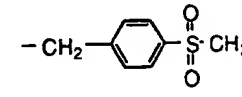
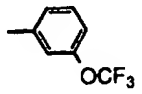
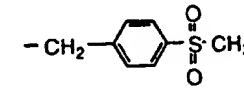
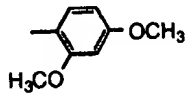
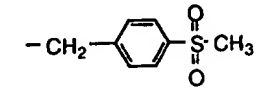
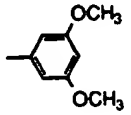
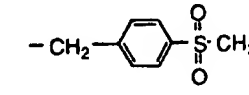
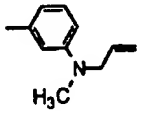
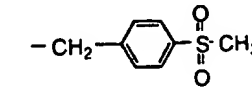
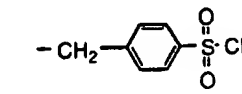
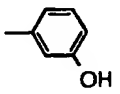
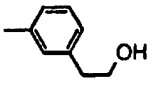
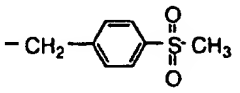
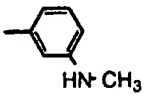
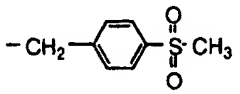
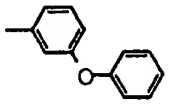
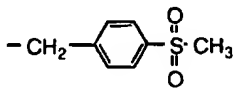
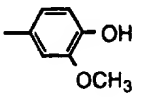
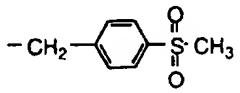
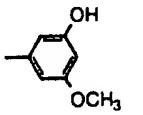
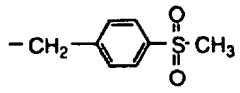
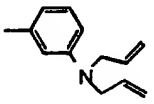
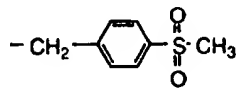
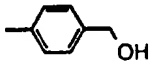
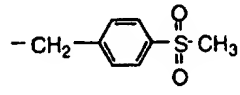
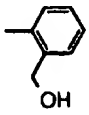
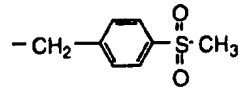
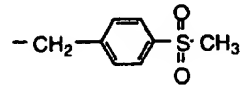
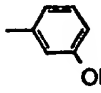
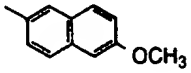
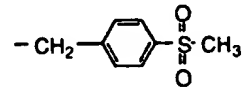
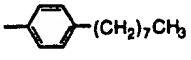
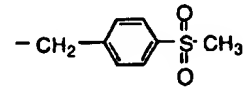
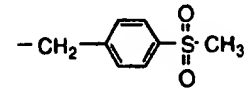
Compound No.	R^1	R^2	R^3	j	k	R^4
121			OH	2	3	
122			OH	2	3	
123			OH	2	3	
124			OH	2	3	
125			OH	2	3	
126			OH	2	3	
127			OH	2	3	
128			OH	2	3	
129			OH	2	3	
130			OH	2	3	
131			OH	2	3	
132			OH	2	3	

Table 1.12

Compound No.	R^1	R^2	R^3	j	k	R^4
133			OH	2	3	
134			OH	2	3	
135			OH	2	3	
136			OH	2	3	
137			OH	2	3	
138			OH	2	3	
139			OH	2	3	
140			OH	2	3	
141			OH	2	3	
142			OH	2	3	
143			OH	2	3	
144			H	2	3	

Tabl 1.13

Compound No.	R^1	R^2	R^3	j	k	R^4
145			OH	2	3	
146			OH	2	3	
147			OH	2	3	
148			OH	2	3	
149			OH	2	3	
150			OH	2	3	
151			OH	2	3	
152			OH	2	3	
153			OH	2	3	
154			OH	2	3	
155			OH	2	3	
156			OH	2	3	

Tabl 1.1 4

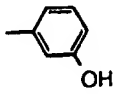
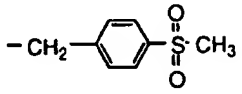
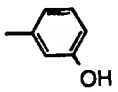
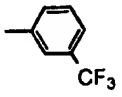
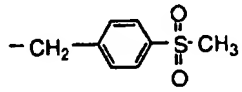
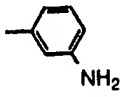
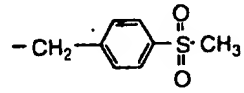
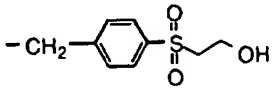
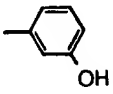
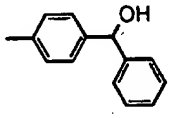
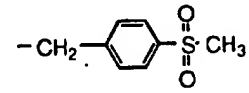
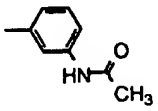
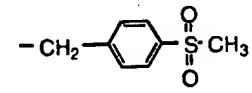
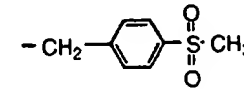
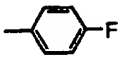
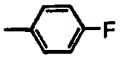
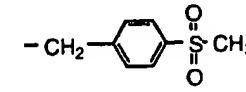
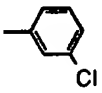
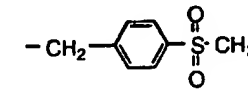
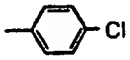
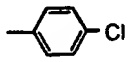
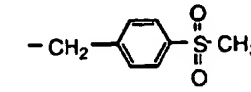
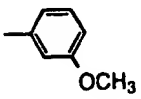
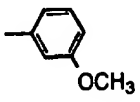
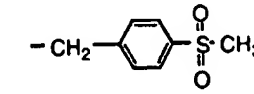
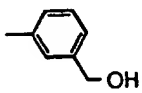
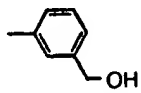
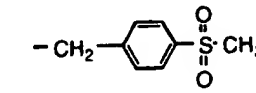
Compound No.	R^1	R^2	R^3	j	k	R^4
157			OH	2	3	
158			OH	2	3	
159			OH	2	3	
160			OH	2	3	
161			OH	2	3	
162			OH	2	3	
163			OH	2	3	
164			OH	2	3	
165			OH	2	3	
166			OH	2	3	
167			OH	2	3	
168			OH	2	3	

Table 1.15

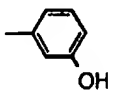
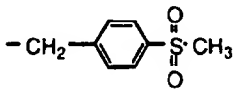
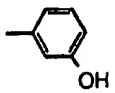
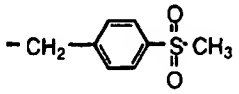
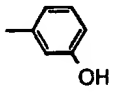
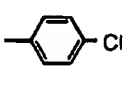
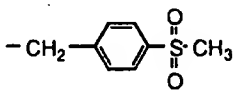
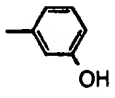
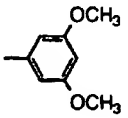
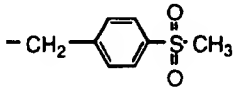
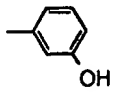
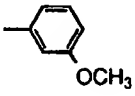
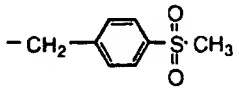
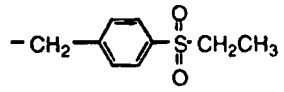
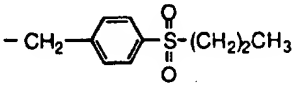
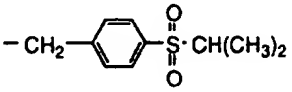
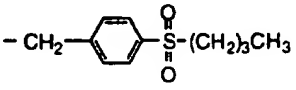
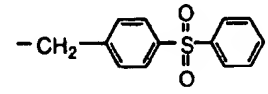
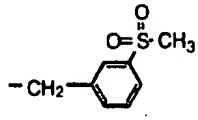
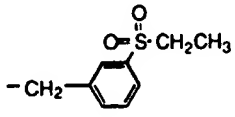
Compound No.	R^1	R^2	R^3	j	k	R^4
169			OH	2	3	
170			OH	2	3	
171			OH	2	3	
172			OH	2	3	
173			OH	2	3	
174			OH	2	3	
175			OH	2	3	
176			OH	2	3	
177			OH	2	3	
178			OH	2	3	
179			OH	2	3	
180			OH	2	3	

Table 1.16

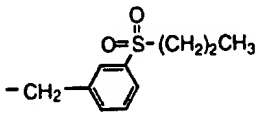
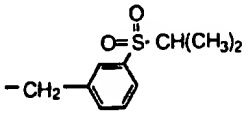
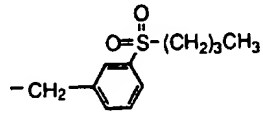
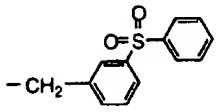
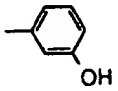
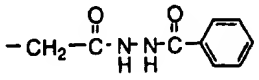
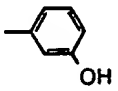
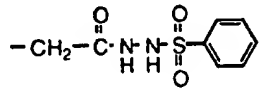
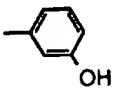
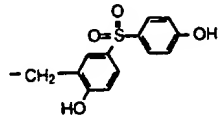
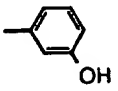
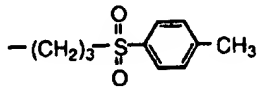
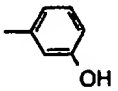
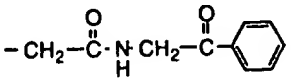
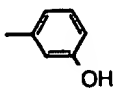
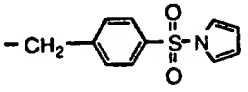
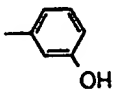
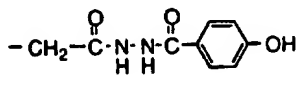
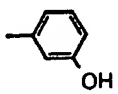
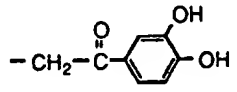
Compound No.	R^1	R^2	R^3	j	k	R^4
181			OH	2	3	
182			OH	2	3	
183			OH	2	3	
184			OH	2	3	
185			OH	2	3	
186			OH	2	3	
187			OH	2	3	
188			OH	2	3	
189			OH	2	3	
190			OH	2	3	
191			OH	2	3	
192			OH	2	3	

Table 1.17

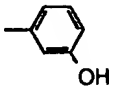
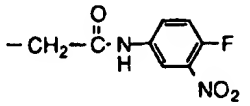
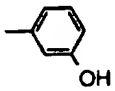
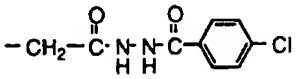
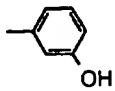
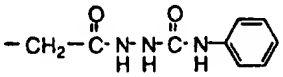
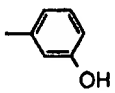
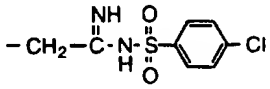
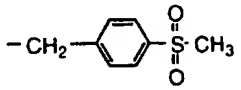
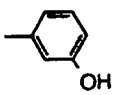
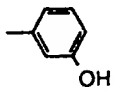
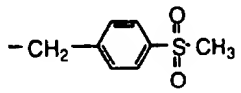
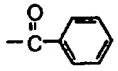
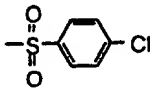
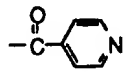
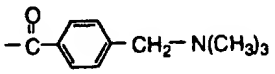
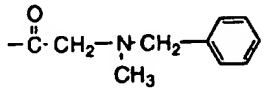
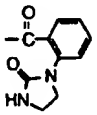
Compound No.	R^1	R^2	R^3	j	k	R^4
193			OH	2	3	
194			OH	2	3	
195			OH	2	3	
196			OH	2	3	
197			OH	3	3	
198			OH	3	3	
199			H	2	3	
200			H	2	3	
201			H	2	3	
202			H	2	3	
203			H	2	3	
204			H	2	3	

Table 1.18

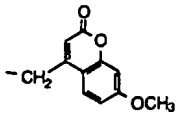
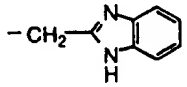
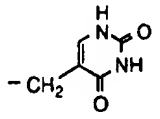
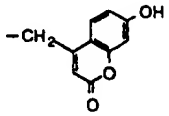
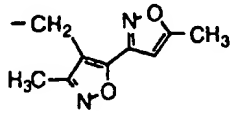
Compound No.	R^1	R^2	R^3	j	k	R^4
205			H	2	3	$-(CH_2)_2CH_3$
206			H	2	3	
207			H	2	3	
208			H	2	3	
209			H	2	3	$-(CH_2)_2-CO_2CH_3$
210			H	2	3	$-CH_2C\equiv CCH_3$
211			H	2	3	
212			H	2	3	
213			H	2	3	$-(CH_2)_4-C\equiv N$
214			H	2	3	$-(CH_2)_2-C\equiv N$
215			H	2	3	$-(CH_2)_3-C\equiv N$
216			H	2	3	

Table 1.19

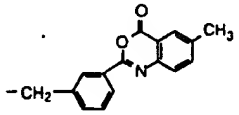
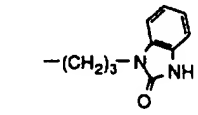
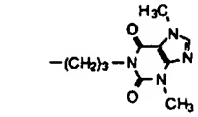
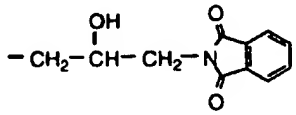
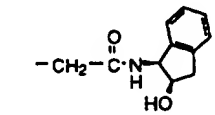
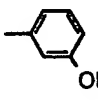
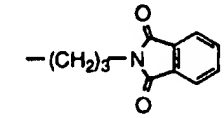
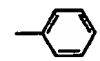
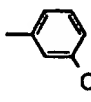
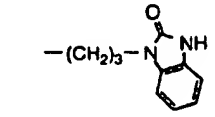
Compound No.	R^1	R^2	R^3	j	k	R^4
217			H	2	3	$-CH_2-C\equiv N$
218			H	2	3	$-CH_2CH(OH)CH_2OCH_2CH_2C\equiv CH$
219			H	2	3	
220			H	2	3	$-CH_2C\equiv CH$
221			H	2	3	
222			H	2	3	$-CH_2CH(CH_3)CH_2OH$
223			H	2	3	
224			H	2	3	$-CH_2-C(=O)-NH-NH-C(=O)-OCH_2CH_3$
225			H	2	3	
226			H	2	3	
227			OH	2	3	
228			OH	2	3	

Table 1.20

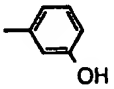
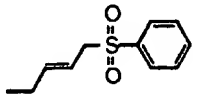
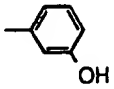
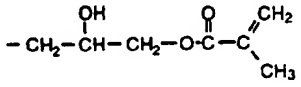
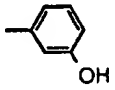
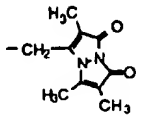
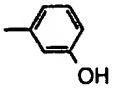
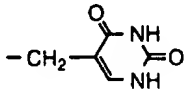
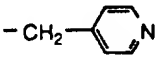
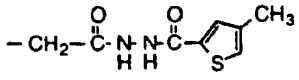
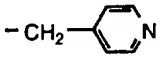
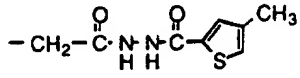
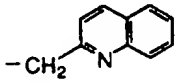
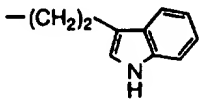
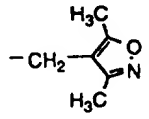
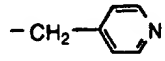
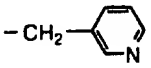
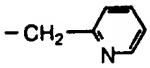
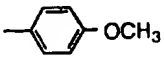
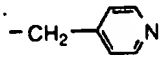
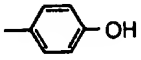
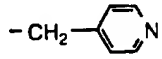
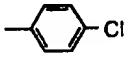
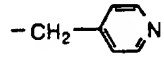
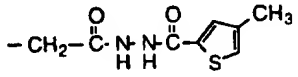
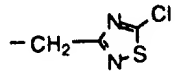
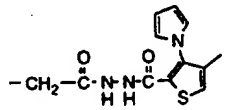
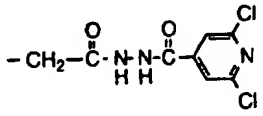
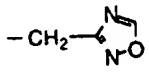
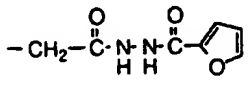
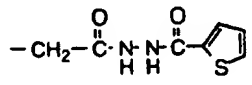
Compound No.	R^1	R^2	R^3	j	k	R^4
229			OH	2	3	
230			OH	2	3	
231			OH	2	3	
232			OH	2	3	
233			CN	2	3	
234			CN	2	3	
235			H	2	2	
236			H	2	2	
237			H	2	3	
238			H	2	3	
239			H	2	3	
240			H	2	3	

Table 1.21

Compound No.	R^1	R^2	R^3	j	k	R^4
241			H	2	3	
242			H	2	3	
243			H	2	3	
244			H	2	3	
245			H	2	3	
246			H	2	3	
247			H	2	3	
248			H	2	3	
249			H	2	3	
250			H	2	3	
251			H	2	3	
252			H	2	3	

Tabl 1.22

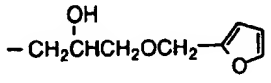
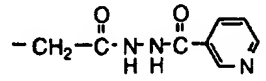
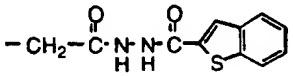
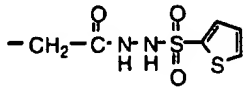
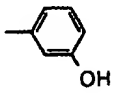
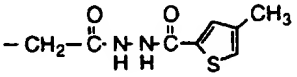
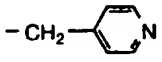
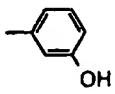
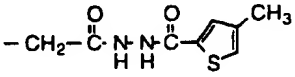
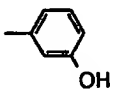
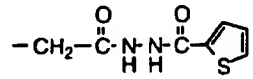
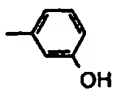
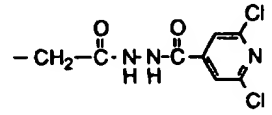
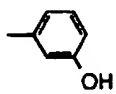
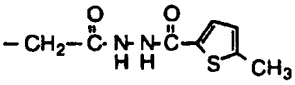
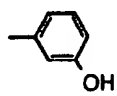
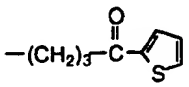
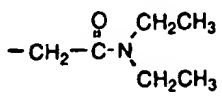
Compound No.	R^1	R^2	R^3	j	k	R^4
253			H	2	3	
254			H	2	3	
255			H	2	3	
256			H	2	3	
257			H	2	3	
258			OH	2	3	
259			OH	2	3	
260			OH	2	3	
261			OH	2	3	
262			OH	2	3	
263			OH	2	3	
264			CN	2	3	

Table 1.23

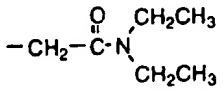
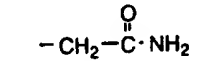
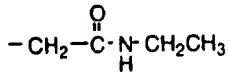
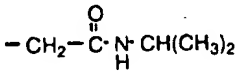
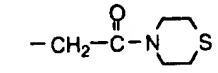
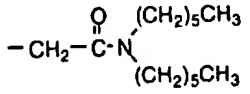
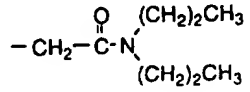
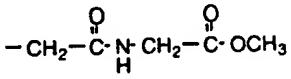
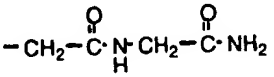
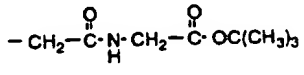
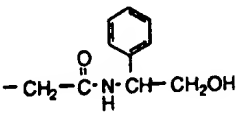
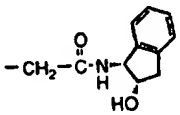
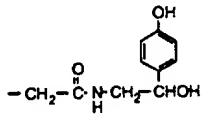
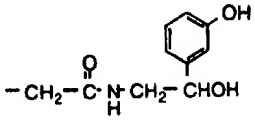
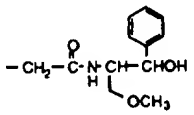
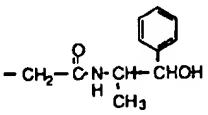
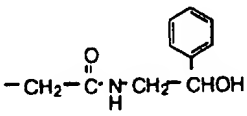
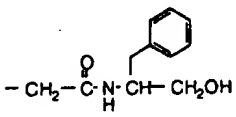
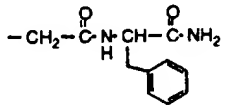
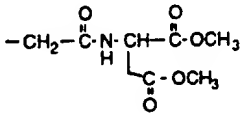
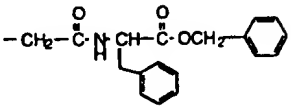
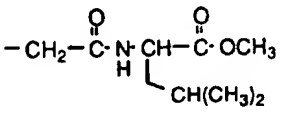
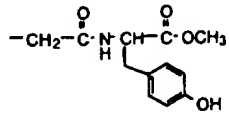
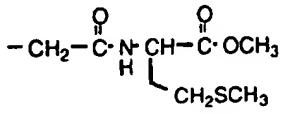
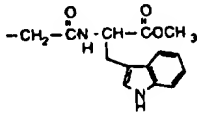
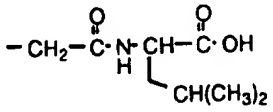
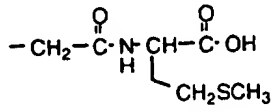
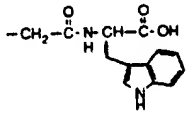
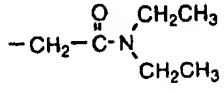
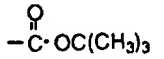
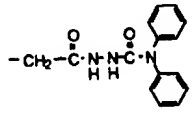
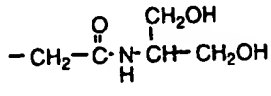
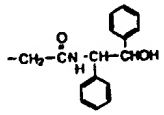
Compound No.	R^1	R^2	R^3	j	k	R^4
265			H	2	3	
266			H	2	3	
267			H	2	3	
268			H	2	3	
269			H	2	3	
270			H	2	3	
271			H	2	3	
272			H	2	3	
273			H	2	3	
274			H	2	3	
275			H	2	3	
276			H	2	3	

Table 1.24

Compound No.	R^1	R^2	R^3	j	k	R^4
277			H	2	3	
278			H	2	3	
279			H	2	3	
280			H	2	3	
281			H	2	3	
282			H	2	3	
283			H	2	3	
284			H	2	3	
285			H	2	3	
286			H	2	3	
287			H	2	3	
288			H	2	3	

Tabl 1.25

Compound No.	R^1	R^2	R^3	j	k	R^4
289			H	2	3	
290			H	2	3	
291			H	2	3	
292			H	2	3	
293			OH	2	3	
294			OH	2	3	
295			OH	2	3	—H
296			OH	2	3	
297			H	2	3	
298			H	2	3	
299			H	2	3	

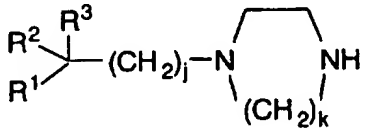
The present invention can also use acid adducts of the cyclic diamine derivatives where such acids include, for example, min ral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, carbonic acid, and the like, as well as organic acids such as citric acid, malic acid, tartaric acid, fumaric acid, methanesulfonic acid, trifluoroacetic acid, and the like.

The present invention may use racemates and all possible optically active forms of the cyclic diamine derivatives represented by the above formula [I] or [II].

Compounds represented by the above general formula [I] and/or [II] can be synthesized by any of the general preparations given below.

(Preparation 1)

A preparation which call for treating one equivalent of a cyclic diamine derivative represented by the formula [III] below :



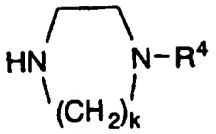
[III]

[where R^1, R^2, R^3, j, and k are as defined respectively in the above formula [I] or [II]] with 0.1-10 equivalents of a compound represented by the formula [IV] below:

$$X^1 - R^4 \qquad [IV]$$

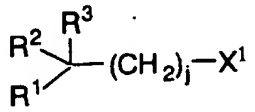
[wherein R^4 is the same as defined for the R^4 in the above formula [I] or [II]; X^1 is a halogen atom, alkylsulfonyloxy group, or arylsulfonyloxy group. R^4 is not a group represented by the formula: $-A^2-R^{11}$ in where A^2 and R^{11} are the same as defined respectively in the above formula [I] or [II]], either in absence or presence of solvent;

alternatively treating 1 equivalent of a cyclic diamine given by the formula [V] below:



[V]

[where R^4 and k are the same as defined respectively in the above formula [I] or [II]], with 0.1-10 equivalents of a compound represented by the formula [VI] below:



[VI]

[where R^1, R^2, R^3, and j are the same as defined respectively in the above formula [I] or [II]; X^1 represents a halogen atom, alkylsulfonyloxy, or arylsulfonyloxy group] either in the absence or presence of solvent.

Such reactions can be more smoothly run if a base is present. The base which may be used includes inorganic salts such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, and the like, or amines such as triethylamine, diisopropylethyl amine, and pyridine, and the like. In addition, the reactions in these preparations can also be promoted by iodide such as potassium iodide, sodium iodide, or the like.

X^1 in the above formulas [IV] and [VI] represents a halogen atom, alkylsulfonyloxy, or arylsulfonyloxy group. Such halogen atoms include preferably chlorine, bromine, and iodine atoms. Suitable specific examples for the alkylsulfonyloxy groups include methylsulfonyloxy and trifluoromethyl sulfonyloxy group and the like. A preferred specific example for the aryl sulfonyloxy group includes a tosyloxy group.

(Preparation 2)

A preparation which calls for treating 1 equivalent of a cyclic diamine derivative represented by the above formula [III] with 0.1-10 equivalents of a carboxylic acid, sulfonic acid represented by the formula [VII] below:

$HO\text{-}A^2\text{-}R^{11}$ [VII]

[where R^{11} and A^2 are the same as defined respectively in the above formulas [I] or [II]], or its reactive derivative, either in the absence or presence of solvent.

The reactive derivatives for the carboxylic acids or sulfonic acids in the above formula [VII] include highly reactive carboxylic or sulfonic acid derivatives, which are usually used in synthetic organic chemistry, such as acid halides, acid anhydrides, mixed acid anhydrides. If esters are used, the reaction can be run smoothly by activating the cyclic diamine derivative represented by the above general formula [III], for example, by using triethylaluminum.

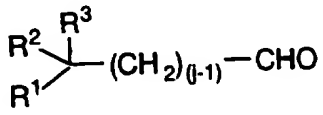
Such reactions can be more smoothly run by using suitable amounts of a dehydrating agent such as molecular sieve, condensing agents such as dicyclohexylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide, carbonyldiimidazole, and the like, or bases similar to those used in the above preparation 1.

(Preparation 3)

A preparation which calls for treating 1 equivalent of a cyclic diamine represented by the above formula [III], with 0.1-10 equivalents of an aldehyde represented by the formula [VIII] below :

$$R^{27}\text{-}(CH_2)_z\text{-}CHO \qquad [VIII]$$

[where in the formula R^{27} represents either R^7, R^{17}, or R^{20} of the above formula [I] or [II]; z represents an integer of 0-3], either in the absence or the presence of solvent under reductive conditions, or else treating 1 equivalent of a compound represented by the above formula [V] with 0.1-10 equivalents of an aldehyde represented by the formula [IX] below :



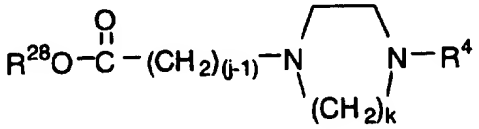
[IX]

[where in the formula R^1, R^2, R^3, and j are the sam as defined respectively in the above formulas [I] or [II]], eith r in the absence or the presence of solvent under reductive conditions.

Such reactions are in general called reductive amination reactions and such reductive conditions may be generated by catalytic hydrogenation using a catalyst containing a metal such as palladium, platinum, nickel, rhodium, or the like, using complex hydrides such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, and the like, boranes, or electrolytic reduction, and the like.

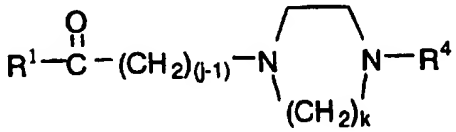
(Preparation 4)

A preparation which calls for treating 1 equivalent of a cyclic diamine derivative represented by the formula [X] below:



[X]

[where in the formula j, k, and R^4 are the same as defined respectively for the above formula [I] or [II] and R^{28} represents a C_1-C_6 lower alkyl group] or 1 equivalent of a cyclic diamine derivative represented by the formula [XI] below:



[XI]

[where R^1, j, k, and R^4 are the same as defined respectively for the above formula [I] or [II]], with 0.1-10 equivalents of an organometallic reagent represented by the formula [XII] below:

R^{29}-M [XII]

[wherein the formula R^{29} is the same as defined for the R^1 and R^2 in the above formula [I] or [II]; M is a metal atom or its halide or complex] in the presence of solvent.

The organometallic reagents used in such preparations may be those suitably selected organometallic reagents known to cause a nucleophilic reaction toward esters and/or ketones in general in synthetic organic chemistry, such as Grignard reagents ($M = MgX^2$), organolithium reagents ($M = Li$), organocerium reagents ($M = CeX^2_2$) (X^2 represents a halogen atom). These organometallic reagents may be prepared by known methods from the corresponding halides. The halides preferably include chlorides, bromides, iodides.

If the substrates submitted to each of the above preparations contains a substituent which reacts under each reaction condition in general in synthetic organic chemistry or is thought to adversely affect the reaction, that functional group can be protected by a known suitable protecting group followed by the reaction of the above preparations and deprotection using a known procedure to obtain the desired compound.

Each of the above preparations may use solvents for the reaction such as halogenated hydrocarbons such as dichloromethane, chloroform, or the like, aromatic hydrocarbons such as benzene, toluene, and the like, ethers such as diethyl ether, tetrahydrofuran, or the like, esters such as ethyl acetate, aprotic polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile, and the like, alcohols such as methanol, ethanol, isopropyl alcohol, and the like.

The reaction temperature in either of the preparations should be in the range of -78 ~ +150 _C, preferably 0 _C ~ 100 _C. After completion of the reaction, the usual isolation and purification operations such as concentration, extraction, recrystallization, chromatography, and the like may be used , to isolate the desired cyclic diamine derivatives represented by the above formula [I] or [II]. These can be converted into pharmacologically acceptable acid adducts by the usual method.

Potential Industrial Utilities

The chemokine receptor antagonist, which contain the cyclic diamine derivative or its pharmacologically acceptable acid adducts of this invention, which inhibits chemokines such as MIP-1α and/ r MCP-1 and the like from action

on target cells, are useful as therapeutic agents and/or preventive preparation for diseases such as atherosclerosis, rheumatic arthritis, psoriasis, asthma, ulcerative colitis, glomerulonephritis, multiple sclerosis, pulmonary fibrosis, myocarditis, and the like, in which tissue infiltration of blood monocytes, lymphocytes, and the like plays a major role in the initiation, progression, and maintenance of the disease.

Examples

The present invention is now specifically described by the following examples. However, the present invention is not limited to these compounds described in these examples. Compound numbers in these examples represent numbers attached to these compounds listed as suitable specific examples in Tables 1.1 - 1.18.

Example 1: Synthesis of 1-(3,3-Diphenylpropyl)-4-(4-nitrobenzyl)homo piperazine (Compound No. 23).

A mixture of 120 mg of homopiperazine, 206 mg of homopiperazine dihydrochloride, and 3 mL of ethanol was heated to 70 _C to prepare a solution. 375 mg of sodium iodide and 287 mg of 3,3-diphenylpropyl methanesulfonate were added sequentially to the solution and the mixture was stirred at 70 _C for 14 hours. The mixture was allowed to cool to room temperature and the ethanol was removed under reduced pressure, followed by adding 20 mL of 2N aqueous sodium hydroxide solution and extracting with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 1-(3,3-diphenylpropyl)homo piperazine.

The resulting 1-(3,3-diphenylpropyl)homopiperazine was dissolved in 3 mL of acetonitrile followed by adding 213 mg of 4-nitrobenzyl bromide and 144 mg of potassium carbonate. The mixture was stirred at 70 _C for 14 hours and allowed to cool to room temperature and the solvent was removed under reduced pressure. 20 mL of aqueous 2N sodium hydroxide was added and the mixture was extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate) to obtain 255 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure; and the residue was dried to obtain the hydrochloride salt of the titled compound.

Compound No. 23 (Free Base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.73-1.82 (m, 2 H), 2.16-2.25 (m, 2 H), 2.40-2.46 (m, 2 H), 2.64-2.71 (m, 8 H), 3.71 (s, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 7.13-7.19 (m, 2 H), 7.19-7.31 (m, 8

H), 7.50 (d, J = 8.6 Hz, 2 H), 8.16 (d, J = 8.6 Hz, 2 H).

Example 2: Preparation of 1-Benzyl-4-(3,3-diphenylpropyl)homopiperazine (Compound No. 15).

A mixture of 101 mg of homopiperazine, 175 mg of homopiperazine dihydrochloride, 3 mL of ethanol was heated to 70 _C into a solution. 0.115 mL of benzyl chloride was added and the mixture was stirred at 70 _C for 3 hours. After cooling to room temperature, ethanol was removed under reduced pressure, and 20 mL of aqueous 2N sodium hydroxide solution was added to the solution, which was extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 1-benzylhomopiperazine.

The resulting benzylhomopiperazine was dissolved in 3 mL of ethanol, to which were added 296 mg of 3,3-diphenylpropyl methanesulfonate and 136 mg of potassium carbonate. The mixture was stirred at 70 _C for 15 hours and it was cooled to room temperature and the solvent was removed under reduced pressure. 20 mL of aqueous 2N sodium hydroxide was added and the solution was extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined and washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate) to obtain 135 mg of the titled compound. This was treated with a hydrogen chloride solution in ether followed by removing the solvent under reduced pressure and drying to give the hydrochloride salt of the titled compound.

Compound No. 15 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.71-1.81 (m, 2 H), 2.16-2.25 (m, 2 H), 2.39-2.45 (m, 2 H), 2.64-2.73 (m, 8 H), 3.62 (s, 2 H), 4.01 (t, J = 7.9 Hz, 1 H), 7.12-7.34 (m, 15 H).

Example 3: Preparation of 1-Benzoyl-4-(3,3-diphenylpropyl)homopiperazine (Compound No. 199).

A mixture of 126 mg of homopiperazine, 218 mg of homopiperazine dihydrochloride, 3 mL of ethanol was heated to 70 _C into a solution. 378 mg of sodium iodide and 289 mg of 3,3-diphenylpropyl methanesulfonate were added sequentially to the solution and the solution was stirred at 70 _C for 15 hours. After the solution was cooled to room temperature, the ethanol was removed under

reduced pressure followed by adding 20 mL of aqueous 2N sodium hydroxide and extracting with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 1-(3,3-diphenylpropyl)homopiperazine .

The resulting 1-(3,3-diphenylpropyl)homopiperazine was dissolved in 3 mL of dichloromethane, followed by adding 107 mg of triethylamine and 140 mg of benzoyl chloride. After the mixture was stirred at room temperature for 6 hours, it was mixed with 20 mL of aqueous 2N sodium hydroxide and extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, hexane/ethyl acetate 4:6) to obtain 249 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure and the residue was dried to give the hydrochloride salt of the titled compound.

Compound No. 199 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.69-1.79 (m, 1 H), 1.90-1.99 (m, 1 H), 2.12-2.28 (m, 2 H), 2.35-2.48 (m, 2 H), 2.54-2.61 (m, 2 H), 2.64-2.69 (m, 1 H), 2.75-2.80 (m, 1 H), 3.39-3.46 (m, 2 H), 3.73-3.78 (m, 2 H), 3.96-4.06 (m, 1 H), 7.13-7.31 (m, 10 H), 7.35-7.39 (m, 5 H).

Example 4: Preparation of 1-[4-(Dimethylaminomethyl) benzoyl]-4-(3,3-diphenylpropyl)homopiperazine (Compound No. 202).

The same method as that of Example 1 was used to obtain 1-(3,3-diphenylpropyl)homopiperazine .

The resulting 1-(3,3-diphenylpropyl)homopiperazine was dissolved in 3 mL of toluene under argon, followed by adding 0.65 mL of a 15% trimethylaluminum solution in hexane. The mixture was stirred at room temperature for 15 minutes, mixed with 187 mg of methyl 4-(dimethylaminomethyl) benzoate, stirred at 60 _C for 22 hours. The mixture was cooled to room temperature, mixed with 2N hydrochloric acid, and stirred. 20 mL of aqueous 2N sodium hydroxide was added and the mixture was extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, concentrat d, and purified by column

chromatography (silica gel, ethyl acetate/methanol 6:4) to btain 234 mg of the titled compound. This was treated with a hydrogen chloride solution in ether, the solvent was removed under reduced pressure and the residue was dried to give the hydrochloride salt of the titled compound.

Compound No. 202 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.65-1.80 (m, 1 H), 1.89-2.01 (m, 1 H), 2.12-2.29 (m, 2 H), 2.24 (s, 6 H), 2.35-2.48 (m, 2 H), 2.52-2.60 (m, 2 H), 2.60-2.70 (m, 1 H), 2.74-2.79 (m, 1 H), 3.40-3.48 (m, 2 H), 3.43 (s, 2 H), 3.32-3.77 (m, 2 H), 3.96-4.06 (m, 1 H), 7.16-7.52 (m, 14 H).

Example 5: Preparation of 1-(3,3-Diphenylpropyl)-4-(2-quinolylmethyl)homopiperazine (Compound No. 237).

The same method as that of Example 1 was used to obtain 1-(3,3-diphenylpropyl)homopiperazine .

The resulting 1-(3,3-diphenylpropyl)homopiperazine was dissolved in 3 mL of ethanol, mixed with 228 mg of 2-(chloromethyl)quinoline hydrochloride and 141 mg of potassium carbonate, and stirred at 70 _C for 14 hours. The mixture was cooled to room temperature and the ethanol was removed under reduced pressure, 20 mL of aqueous 2N sodium hydroxide was added and the mixture was extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate/methanol 95:5), to obtain 109 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure and the residue was dried to give the hydrochloride salt of the titled compound.

Compound No. 237 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.76-1.86 (m, 2 H), 2.18-2.27 (m, 2 H), 2.42-2.49 (m, 2 H), 2.68-2.82 (m, 8 H), 3.96 (s, 2 H), 4.02 (t, J = 7.6 Hz, 1 H), 7.12-7.31 (m, 1 H), 7.50 (dd, j = 7.9, 7.9 Hz, 1 H), 7.65-7.72 (m, 2 H), 7.79 (d, J = 7.9 Hz, 1 H), 8.05 (d, J = 8.3 Hz, 1 H), 8.11 (d, J = 8.6 Hz, 1 H).

Example 6: Preparation of 1-(3,3-Diphenylpropyl)-4-(7-methoxy-2*H*-chromene-2-one-4-ylmethyl)homopiperazine (Compound No. 206).

The same method as that of Example 5 was used except for the use of 70

mg of 4-(bromomethyl)-7-methoxy-2 *H*-chromene-2-one to give 303 mg of the titled compound, and except for the use of ethanol/chloroform as the s lvent for the reaction. Furthermore, the same method as that of Example 5 was used to obtain the hydrochloride salt of the titled compound.

Compound No. 206 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm) : 1.75-1.85 (m, 2 H), 2.16-2.25 (m, 2 H), 2.39-2.45 (m, 2 H), 2.62-2.79 (m, 8 H), 3.72 (s, 2 H), 3.87 (s, 3 H), 4.02 (t, J = 7.6 Hz, 1 H), 6.36 (s, 1 H), 6.80-6.85 (m, 2 H), 7.12-7.31 (m, 10 H), 7.75 (d, J = 9.6 Hz, 1 H).

Example 7: Preparation of 1-(2-Benzimidazolylmethyl)-4-(3,3-diphenylpropyl)homopiperazine (Compound No. 207).

The same method as that of Example 5 was used except for the use of 165 mg of 2-(chloromethyl)benzimidazole and 16 mg of sodium iodide to promote the reaction to give 91 mg of the titled compound. Furthermore, the same method as that of Example 5 was used to obtain the hydrochloride salt of the titled compound.

Compound No. 207 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.70-1.82 (m, 2 H), 2.19-2.29 (m, 2 H), 2.43-2.50 (m, 2 H), 2.65-2.73 (m, 4 H), 2.76-2.81 (m, 4 H), 3.96 (s, 2 H), 3.99 (t, J = 7.6 Hz, 1 H), 7.14-7.31 (m, 14 H), 7.60-7.85 (m, 1 H).

Example 8: Preparation of 1-(2,2-Diphenyl ethyl)-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 6).

A mixture of 120 mg of homopiperazine, 216 mg of homopiperazine dihydrochloride salt, 3 mL of ethanol was heated to 70 _C into a solution. To this solution were added sequentially 383 mg of sodium iodide and 250 mg of 4-(methylsulfonyl)benzyl bromide, followed by stirring at 70 _C for 14 hours. After the solution was cooled to room temperature, ethanol was removed under reduced pressure and 20 mL of aqueous 2N sodium hydroxide was added and the mixture was extracted with 20 mL x 2 of ethyl acetate. The organic layers were combined, washed with 20 mL of aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 176 mg of 1-[4-(methylsulfonyl)benzyl]homopiperazine .

The resulting 1-[4-(methylsulfonyl)benzyl]homopiperazine was dissolved in 5 mL of dichloromethane, followed by adding 223 mg of diphenylacetaldehyde and 217 mg of sodium triacetoxyborohydride. After the mixture was stirred at room temperature for 16 hours, it was mixed with 30 mL of aqueous saturated sodium hydrogencarbonate, and extracted with 30 mL x 2 of ethyl acetate. The organic layers were combined, washed with 30 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate) to obtain 173 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure, the residue was dried to give the hydrochloride salt of the titled compound.

Compound No. 6 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.64-1.77 (m, 2 H), 2.51-2.64 (m, 4 H), 2.67-2.83 (m, 4 H), 3.04 (S, 3 H), 3.15 (d, J = 7.6 Hz, 2 H), 3.61 (s, 2 H), 4.14 (t, J = 7.6 Hz, 1 H), 7.13-7.35 (m, 10 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.84 (d, J = 8.2 Hz, 2 H).

Example 9: Preparation of 1-(3-Hydroxy-3,3-diphenylpropyl)-4-(4-chlorobenzyl)homopiperazine (Compound No. 107).

A solution of 54 mg of methyl 3-[4-(4-chlorobenzyl) homopiperazinyl] propionate in 10 mL of ether was mixed with under nitrogen, 4 mL of 1 M phenyl magnesium bromide. The mixture was stirred at room temperature for 30 minutes, mixed with aqueous saturated ammonium chloride and the mixture was extracted with 50 mL of ethyl acetate. The extract was washed with 50 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate/methanol 9:1) to give 65 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure and the residue was dried to give the hydrochloride salt of the titled compound.

Compound 107 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.77-1.86 (m, 2 H), 2.36-2.40 (m, 2 H), 2.54-2.71 (m, 10 H), 3.58 (s, 2 H), 7.15-7.20 (m, 2 H), 7.26-7.32 (m, 8 H), 7.44-7.48 (m, 4 H).

Example 10: Preparation of 1-(3,3-Diphenylpropyl)-4-(4-carbamoylbenzyl)homopiperazine (Compound No. 55).

A 20 mL solution of 175 mg of compound No. 30 in 20 mL of t-butyl alcohol was mixed with 570 mg of ground potassium hydroxide and the mixture was refluxed for 2.5 hours. The solution was cooled to room temperature and mixed with 50 mL of water and 100 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted with 50 mL of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate/methanol 4:1) to give 91 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure and the residue was dried to give the hydrochloride salt of the titled compound.

Compound No. 55 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 0.86-0.91 (m, 1 H), 1.23-1.28 (m, 2 H), 1.73-1.82 (m, 2 H), 2.18-2.26 (m, 2 H), 2.42-2.47 (m, 2 H), 2.65-2.73 (m, 6 H), 3.67 (s, 2 H), 5.6-6.2 (brs, 2 H), 7.13-7.30 (m, 10 H), 7.41 (d, 2 H, J = 8.25 Hz), 7.75 (d, 2 H, J = 8.25 Hz).

Example 11: Preparation of 1-[3,3-Di(2-furyl)-3-hydroxypropyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 129).

To a solution of 2-furyl lithium prepared in 50 mL of THF using 3 mL of furan and 2 mL of 1.63 M n-butyllithium was added dropwise at 0 °C, a 10 mL solution in THF of 99 mg of methyl 3-[4-{4-(methylsulfonyl)benzyl}homopiperazinyl] propionate. After stirring at 0 °C for 1 hour, the mixture was mixed with 50 mL of an aqueous saturated ammonium chloride, and extracted with 50 mL x 2 of ethyl acetate. The extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate) to give 62 mg of the titled compound.

Compound No. 129 had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.80-1.89 (m, 2 H), 2.32-2.36 (m, 2 H), 2.56-2.60 (m, 2 H), 2.74-2.78 (m, 2 H), 2.66-2.70 (m, 6 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 6.30-6.34 (m, 4 H), 7.36-7.37 (m, 2 H), 7.55 (d, 2 H J = 8.25 Hz), 7.86 (d, 2 H, J = 8.25 Hz).

Example 12: Preparation of 1-[3,3-Bis(4-hydroxyphenyl)-3-hydroxypropyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 119).

To a 2.0 mL anhydrous THF solution of 120 mg of methyl 3-[4-(4-chlorobenzyl)homopiperazinyl]propionate was added under nitrogen, 2.0 mL solution in THF of 1.5 mmol of 4-(*tert*-butyldimethylsilyloxy)phenyl magnesium

bromide. The mixture was stirred at room temperature for 30 minutes and an aqu us saturated ammonium chloride solution was added and the mixture was extracted with 20 mL x 3 of ethyl acetate. The extracts were washed with aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to give 33 mg of a silyl protected form of the titled compound. The resulting oily product was dissolved in 3 mL of THF and mixed with 0.8 mL of a 1N THF solution of tributylammonium fluoride. The mixture was stirred at room temperature for 4 hours, mixed with aqueous saturated ammonium chloride and extracted with 20 mL x 3 of ethyl acetate. The extracts were washed with aqueous saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography to obtain 5 mg of the titled compound.

Compound No. 119 had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.81-1.94 (m, 2 H), 2.35 (broad s, 3 H), 2.55-2.82 (m, 1 H), 3.08 (s, 3 H), 3.70 (s, 2 H), 6.67 (d, J = 8.6 Hz, 4 H), 7.14 (d, J = 8.9 Hz, 4 H), 7.48 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H).

Example 13: Preparation of 1-[3-Hydroxy-3-(1-methyl-2-pyrrolyl) -3-phenylpropyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 136).

1.0 mL of an anhydrous THF solution of 121 mg of methyl 3-[4-{4-(methylsulfonyl)benzyl}homo piperazinyl]propionate was added under nitrogen to 6 mL of a THF solution of 1.5 mmol of 1-methyl-2-pyrrolyl cerium dichloride at -78 °C. After stirring at -78 °C for 3 hours, the mixture was mixed with 20 mL of water and it was filtered from insoluble matter using Celite, followed by extracting the filtrate with 30 mL x 2 of ethyl acetate. The extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate, ethyl acetate/methanol 10:1) to give 7 mg of the titled compound.

Compound No. 136 had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 7.88 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.32-7.16 (m, 5 H), 6.48-6.47 (m, 1 H), 6.22-6.20 (m, 1 H), 6.06-6.04 (m, 1 H), 3.72 (s, 2 H), 3.26 (s, 3 H), 3.06 (s, 3 H), 2.87-2.39 (m, 11 H), 2.05-1.83 (m, 3 H).

Example 14: Preparation of 1-[3,3-Bis(1-methyl-2-pyrrolyl)-3-

hydroxypropyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 127).

2.0 mL of an anhydrous THF solution of 160 mg of 1-[4-(methylsulfonyl)benzyl]-4-(3-oxo-3-phenylpropyl)homopiperazine was added under nitrogen at -78 °C to a 3 mL THF solution of 0.8 mmol of 1-methyl-2-pyrrolylcerium dichloride. The mixture was stirred at -78 °C for 3 hours and then it was mixed with 20 mL of water and filtered from insolubles, using Celite; the filtrate was extracted with 30 mL x 2 of ethyl acetate. The extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, hexane/ethyl acetate 1:3, ethyl acetate) to give 18 mg of the titled compound.

Compound No. 127 had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 7.88 (d, J = 8.3 Hz, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 6.50-6.48 (m, 2 H), 6.24-6.22 (m, 2 H), 6.03-6.00 (m, 2 H), 3.71 (s, 2 H), 3.21 (s, 6 H), 3.05 (s, 3 H), 2.8-2.62 (m, 10 H), 2.36-2.32 (m, 2 H), 1.88-1.83 (m, 2 H).

Example 15: Preparation of 1-(3,5-Difluorophenyl)-3-hydroxy-3-(3-hydroxyphenyl)propyl-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 138).

To 1.0 mL anhydrous THF solution of 263 mg of 1-[4-(methylsulfonyl)benzyl]-4-[3-oxo-3-{3-(tert-butyldimethylsilyloxy)phenyl}propyl]homopiperazine was added 3 mL of a THF solution of 2.5 mmol of 3,5-difluorophenylmagnesium bromide under nitrogen at 0 °C. The mixture was stirred at room temperature for 3 hours, and aqueous saturated ammonium chloride was added and the mixture was extracted with 40 mL x 2 with ethyl acetate. The extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate, ethyl acetate/methanol 10:1) to obtain 11 mg of a silyl protected form of the titled compound.

The resulting oil was dissolved in 5 mL of THF and mixed with 0.07 mL of a THF solution of 1 M tetrabutylammonium fluoride. The mixture was stirred at room temperature for 30 minutes and mixed with 20 mL of water and extracted with 30 mL x 3 of ethyl acetate. The extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate) to give 11 mg of the titled compound.

Comp und No. 138 had the foll wing ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 7.88 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 8.3 Hz, 2 H), 7.18 (t, J = 7.9 Hz, 1 H), 7.02-6.93 (m, 4 H), 6.70-6.58 (m, 1 H), 3.68 (s, 2 H), 3.06 (s, 3 H), 2.72-2.60 (m, 10 H), 2.33-2.28 (m, 2 H), 1.85-1.76 (m, 2 H).

Example 16: Preparation of 1-[3-(4-Hydroxyphenyl)-3-phenyl propyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 42).

5.0 mL solution in dichloromethane of 33 mg of 1-[3-(4-methoxyphenyl)3-phenyl propyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine was cooled under nitrogen to -78 °C, followed by adding 0.022 mL of boron tribromide. The mixture was gradually allowed to rise to room temperature, at which temperature the mixture was stirred for 3 hours, followed by adding 3 mL of an aqueous saturated sodium hydrogencarbonate solution and extracting with a 50 mL x 2 of ethyl acetate. The extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (silica gel, ethyl acetate/methanol 9:1) to obtain 12 mg of the titled compound. This was treated with a hydrogen chloride solution in ether and the solvent was removed under reduced pressure and residue was dried to give the hydrochloride salt of the titled compound.

Compound No. 42 (free base) had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.75-1.8 (m, 2 H), 2.15-2.3 (m, 2 H), 2.4-2.9 (m, 10 H), 3.04 (s, 3 H), 3.68 (s, 2 H), 3.82 (t, J = 7.5 Hz, 1 H), 6.59 (d, J = 8.6 Hz, 2 H), 7.1-7.3 (m, 5 H), 7.51 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H).

Example 17: Preparation of 1-[3-Hydroxy-3-(3-methylaminophenyl)-3-phenylpropyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 146).

To a solution of 34 mg of compound No. 143 in 1.2 mL of acetonitrile and 0.3 mL of water was added 14 mg of $RhCl(PPh_3)_3$, and the mixture was stirred at 100 _C for 2 days. After the mixture was allowed to cool to room temperature, evaporation of acetonitrile and column chromatography (silica gel, ethyl acetate) gave 9.0 mg of the titled compound.

Compound No. 146 had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 1.79–1.91 (m, 2 H), 2.34–2.41 (m, 2 H), 2.55–2.75 (m, 11 H), 2.80 (s, 3 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 5.40 (broad s, 1 H), 6.39–6.44 (m, 1 H), 6.70–6.80 (m, 2 H), 7.05–7.20 (m, 2 H), 7.21–7.31 (m, 3 H), 7.41–7.48 (m, 2 H), 7.55 (d, J

= 8.1 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 2 H).

Example 18: Preparation of 1-[3-(3-Acetylaminophenyl)-3-hydroxy-3-phenylpropyl]-4-[4-(methylsulfonyl)benzyl]homopiperazine (Compound No. 162).

To a solution of 352 mg of compound No. 159 in 5 mL of dichloromethane was added 190 µL of triethylamine and 130 µL of acetic anhydride. The mixture was stirred at room temperature for 2 hours. 3 mL of water was added and the mixture was extracted with dichloromethane. The extract was concentrated and purified by column chromatography (silica gel, ethyl acetate/methanol 7:3) to give 224 mg of the titled compound as a white solid.

Compound No. 162 had the following ^{1}H NMR ($CDCl_3$, 270 MHz) δ (ppm): 7.88 (d, J = 8.3 Hz, 2 H), 7.57-7.45 (m, 5 H), 7.22-7.16 (m, 6 H), 3.70 (s, 2 H), 3.05 (s, 3 H), 2.73-2.60 (m, 10 H), 2.40-2.37 (m, 2 H),1.88-1.81 (m, 2 H) .

Examples 19-151.

The compounds of this invention were synthesized pursuant to methods of Example 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 14, 15, or 16, using the corresponding reactant respectively. The ^{1}H NMR data, yields, and synthetic methods are summarized in Table 2.

--- Table 2 (~~24~~ 22 pages)---

Table 2

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic meth d
Example 19	5	1.69-1.82 (m, 2 H), 2.58-2.70 (m, 4 H), 2.69 (t, J = 5.9 Hz, 2 H), 2.76 (t, J = 5.9 Hz, 2 H), 3.04 (s, 3 H), 3.73 (s, 2 H), 4.61 (s, 1 H), 7.11-7.21 (m, 2 H), 7.26 (dd, J =7.3, 7.3 Hz, 4 H), 7.42 (d, J = 7.3 Hz, 4 H), 7.56 (d, J = 8.6 Hz, 2 H), 7.87 (d, J = 8.6 Hz, 2 H).	47	Similar to Example 2
Example 20	7	2.15-2.35 (m, 4 H), 2.35-2.60 (m, 8 H), 3.04 (s, 3 H), 3.57 (s, 2 H), 3.97 (t, J = 7.3 Hz, 1 H), 7.10-7.34 (m, 10 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H).	44	Similar to Example 1
Example 21	8	2.15-2.33 (m, 4 H), 2.33-2.55 (m, 8 H), 3.45 (s, 2 H), 3.96 (t, J = 6.9 Hz, 1 H), 7.10-7.33 (m, 14 H).	54	Similar to Example 1
Exampl 22	16	1.78-1.88 (m, 2 H), 2.18-2.27 (m, 2 H), 2.42-2.49 (m, 2 H), 2.66-2.74 (m, 4 H), 2.78-2.87 (m, 4 H), 3.26 (s, 2 H), 4.03 (t, J = 7.6 Hz, 1 H), 7.07-7.37 (m, 13 H), 7.57 (d, J = 7.6 Hz, 2 H), 9.31 (br.s, 1 H).	33	Similar to Example 1
Example 23	17	1.61-1.71 (m, 2 H), 2.14-2.23 (m, 2 H), 2.35-2.41 (m, 2 H), 2.45-2.65 (m, 10 H), 2.93 (t, J = 5.3 Hz, 2 H), 3.99 (t, J = 7.6 Hz, 1 H), 5.30 (s, 1 H), 7.13-7.31 (m, 10 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.80 (d, J = 8.6Hz, 2 H).	21	Similar to Example 1
Example 24	18	1.67-1.77 (m, 2 H), 2.12-2.24 (m, 2 H), 2.35-2.41 (m, 2 H), 2.55-2.64 (m, 4 H), 2.69-2.77 (m, 4 H), 3.19 (s, 2 H), 3.98 (t, J = 7.6 Hz, 1 H), 4.47 (d, J = 5.9 Hz, 2 H), 7.13-7.35 (m, 10 H), 7.63 (br, 1 H).	43	Similar to Example 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synth tic method
Example 25	19	1.76-1.85 (m, 2 H), 2.19-2.28 (m, 2 H), 2.41-2.48 (m, 2 H), 2.65-2.75 (m, 4 H), 2.81-2.87 (m, 4 H), 2.96 (t, J = 5.9 Hz, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 4.06 (t, J = 5.9 Hz, 2 H), 6.88-6.97 (m, 3 H), 7.12-7.21 (m, 2 H), 7.21-7.31 (m, 10 H).	51	Similar to Example 1
Example 26	20	1.68-1.78 (m, 2 H), 2.16-2.25 (m, 2 H), 2.36-2.43 (m, 2 H), 2.55-2.71 (m, 10 H), 3.28 (dt, J = 5.9, 5.0 Hz, 2 H), 3.97 (t, J = 7.6 Hz, 1 H), 5.55 (br, 1 H), 6.99-7.05 (m, 1 H), 7.13 (d, J = 7.34 Hz, 15 H).	13	Similar t Example 1
Example 27	21	1.82-1.93 (m, 2 H), 2.19-2.28 (m, 2 H), 2.43-2.50 (m, 2 H), 2.68-2.81 (m, 10 H), 3.52 (dt, J = 5.6, 5.0 Hz, 2 H), 3.99 (t, J = 7.6 Hz, 1 H), 7.08 (br, 1 H), 7.14-7.31 (m, 10 H), 7.38-7.52 (m, 3 H), 7.81 (d, J = 6.6 Hz, 2 H).	19	Similar to Example 1
Example 28	22	1.78-1.87 (m, 2 H), 2.21-2.30 (m, 2 H), 2.43-2.50 (m, 2 H), 2.68-2.74 (m, 4 H), 2.81-2.88 (m, 4 H), 3.44 (s, 2 H), 3.99 (t, J = 7.6 Hz, 1 H), 5.14 (s, 2 H), 7.12-7.40 (m, 15 H).	25	Similar to Example 1
Example 29	24	1.73-1.83 (m, 2 H), 2.17-2.26 (m, 2 H), 2.41-2.47 (m, 2 H), 2.63-2.73 (m, 8 H), 3.72 (s, 2 H), 4.02 (t, J = 7.6 Hz, 1 H), 7.12-7.20 (m, 2 H), 7.20-7.31 (m, 8 H), 7.46 (dd, J = 7.9, 7.9 Hz, 1 H), 7.67 (d, J = 7.9 Hz, 2 H), 8.09 (dd, J = 7.9, 1.0 Hz, 1 H), 8.21 (s, 1 H).	50	Similar to Example 1
Example 30	25	1.70-1.74 (m, 2 H), 2.16-2.21 (m, 2 H), 2.37-2.41 (m, 2 H), 2.54-2.57 (m, 2 H), 2.59-2.66 (m, 6 H), 3.89 (s, 2 H), 4.01 (t, J = 7.7 Hz, 1 H), 7.13-7.17 (m, 2 H), 7.23-7.28 (m, 8 H), 7.34-7.37 (m, 1 H), 7.48-7.51 (m, 1 H), 7.56 (d, J = 7.7 Hz, 1 H), 7.76 (dd, J = 8.1, 1.1 Hz, 1 H).	58	Similar to Exampl 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 31	26	1.73-1.80 (m, 2 H), 2.18-2.25 (m, 2 H), 2.41-2.45 (m, 2 H), 2.64-2.71 (m, 8 H), 3.57 (s, 2 H), 3.79 (s, 3 H), 4.00 (t, J = 7.8 Hz, 1 H), 6.84 (d, J = 8.8Hz, 2 H), 7.13-7.18 (m, 2 H), 7.21-7.28 (m, 10 H).	31	Similar to Example 1
Example 32	27	1.74-1.80 (m, 2 H), 2.18-2.24 (m, 2 H), 2.40-2.45 (m, 2 H), 2.62-2.71 (m, 8 H), 3.61 (s, 2 H), 3.80 (s, 3 H), 4.01 (t, J = 7.8 Hz, 1 H), 6.77 (dd, J = 8.3, 2.4 Hz, 1 H), 6.88-6.91 (m, 2 H), 7.13-7.19 (m, 2 H), 7.20-7.29 (m, 9 H).	37	Similar to Example 1
Example 33	28	1.78-1.87 (m, 2 H), 2.19-2.27 (m, 2 H), 2.39-2.48 (m, 2 H), 2.63-2.81 (m, 8 H), 3.71 (s, 2 H), 3.81 (s, 3 H), 4.01 (t, J = 7.8 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.93 (dd, J = 7.3, 7.3 Hz, 1 H), 7.13-7.18 (m, 2 H), 7.19-7.29 (m, 9 H), 7.40 (d, J = 7.8 Hz, 1 H).	43	Similar to Example 1
Example 34	29	1.87-1.94 (m, 2 H), 2.17-2.25 (m, 2 H), 2.37-2.42 (m, 2 H), 2.60-2.65 (m, 2 H), 2.70-2.75 (m, 2 H), 3.28-3.34 (m, 2 H), 3.35-3.40 (m, 2 H), 3.99 (t, J = 7.8 Hz, 1 H), 6.77 (ddd, J = 8.3, 6.8, 1.0 Hz, 1 H), 7.02 (dd, J = 8.8, 1.0 Hz, 1 H), 7.14-7.19 (m, 2 H), 7.20-7.29 (m, 8 H), 7.35 (ddd, J = 8.8, 6.8, 1.5 Hz, 1 H), 7.71 (dd, J = 8.3, 1.5 Hz, 1 H).	45	Similar to Example 1
Example 35	30	1.7-1.85 (m, 2 H), 2.15-2.3 (m, 2 H), 2.4-2.5 (m, 2 H), 2.6-2.75 (m, 8 H), 3.67 (s, 2 H), 4.01 (t, J = 7.5 Hz, 1 H), 7.1-7.35 (m, 10 H), 7.44 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 8.3 Hz, 2 H).	38	Similar to Exampl 1
Exampl 36	31	1.7-1.85 (m, 2 H), 2.15-2.3 (m, 2 H), 2.4-2.5 (m, 2 H), 2.6-2.75 (m, 8 H), 3.66 (s, 2 H), 4.01 (t, J = 7.5 Hz, 1 H), 7.1-7.35 (m, 10 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H).	30	Similar to Exampl 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic m thod
Exampl 37	32	1.75-1.88 (m, 2 H), 2.20-2.32 (m, 2 H), 2.39-2.50 (m, 2 H), 2.62-2.90 (m, 12 H), 4.00 (t, J = 7.6 Hz, 1 H), 7.11-7.25 (m, 10 H), 7.34 (d, J = 8.6 Hz, 2 H), 8.13 (d, J = 8.6 Hz, 2 H).	53	Similar to Example 1
Example 38	33	1.73-1.89 (m, 4 H), 2.16-2.27 (m, 2 H), 2.39-2.47 (m, 2 H), 2.48 (t, J = 7.3 Hz, 2 H), 2.58-2.70 (m, 8 H), 2.73 (t, J = 7.3 Hz, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 7.12-7.20 (m, 2 H), 7.20-7.30 (m, 8 H), 7.33 (d, J = 8.6 Hz, 2 H), 8.13 (d, J = 8.6 Hz, 2 H).	55	Similar to Example 1
Example 39	34	1.75-1.85 (m, 2 H), 2.2-2.35 (m, 2 H), 2.45-2.55 (m, 2 H), 2.6-2.8 (m, 8 H), 3.58 (s, 2 H), 3.99 (t, J = 7.5 Hz, 1 H), 7.1-7.35 (m, 14 H).	26	Similar to Example 1
Exampl 40	35	1.7-1.85 (m, 2 H), 2.15-2.3 (m, 2 H), 2.4-2.5 (m, 2 H), 2.6-2.75 (m, 8 H), 3.66 (s, 2 H), 3.95 (s, 3 H), 4.02 (t, J = 7.5 Hz, 1 H), 6.96 (d, J = 6.9 Hz, 1 H), 7.1-7.35 (m, 11 H), 7.81 (d, J = 8.2 Hz, 1 H).	48	Similar to Example 1
Example 41	36	1.73-1.86 (m, 2 H), 2.15-2.29 (m, 2 H), 2.40-2.51 (m, 2 H), 2.55-2.71 (m, 8 H), 3.04 (s, 3 H), 3.71 (s, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 7.11-7.32 (m, 10 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	57	Similar to Exampl 1
Example 42	37	1.72-1.84 (m, 2 H), 2.16-2.28 (m, 2 H), 2.39-2.48 (m, 2 H), 2.61-2.74 (m, 8 H), 3.74 (s, 2 H), 3.90 (s, 3 H), 4.01 (t, J = 7.6 Hz, 1 H), 7.11-7.20 (m, 2 H), 7.20-7.31 (m, 8 H), 7.40 (d, J = 8.3 Hz, 2 H), 7.97 (d, J= 8.3 Hz, 2 H).	37	Similar t Example 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 43	38	1.7-1.75 (m, 2 H), 2.15-2.25 (m, 2 H), 2.29 (s, 3 H), 2.4-2.5 (m, 2 H), 2.6-2.77 (m, 8 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 3.97 (t, J = 7.6 Hz, 1 H), 7.03-7.33 (m, 9 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H).	10	Similar t Exampl 1
Example 44	39	1.7-1.75 (m, 2 H), 2.15-2.25 (m, 2 H), 2.30 (s, 3 H), 2.4-2.5 (m, 2 H), 2.6-2.8 (m, 8 H), 3.04 (s, 3 H), 3.70 (s, 2 H), 3.96 (t, J = 7.6 Hz, 1 H), 6.9-7.3 (m, 9 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H).	26	Similar to Example 1
Example 45	40	1.75-1.88 (m, 2 H), 2.12- 2.22 (m, 2 H), 2.28 (s, 3 H), 2.4-2.6 (m, 2 H), 2.6-2.85 (m, 8 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 4.23 (t, J = 7.6 Hz, 1 H), 7.1-7.3 (m, 8 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.88 (d, J = 8.2 Hz, 2 H).	26	Similar to Example 1
Example 46	41	1.7-1.85 (m, 2 H), 2.1-2.25 (m, 2 H), 2.35-2.5 (m, 2 H), 2.55-2.75 (m, 8 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 3.76 (s, 3 H), 3.95 (t, J = 7.7 Hz, 1 H), 6.81 (d, J = 8.6 Hz, 1 H), 7.1-7.3 (m, 7 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	19	Similar to Exampl 1
Exampl 47	43	1.75-1.85 (m, 2 H), 2.13-2.15 (m, 2 H), 2.41 (t, J = 7.3 Hz, 2 H), 2.58-2.74 (m, 8 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 4.00 (t, J = 7.7 Hz, 1 H), 7.12-7.31 (m, 9 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	40	Similar to Example 1
Example 48	44	1.7-1.85 (m, 2 H), 2.12-2.25 (m, 2 H), 2.44 (t, J = 7 Hz, 2 H), 2.55-2.75 (m, 8 H), 3.58 (s, 2 H), 3.76 (s, 3 H), 3.95 (t, J = 7.7 Hz, 1 H), 6.81 (d, J = 8.8 Hz, 2 H), 7.15 (d, J = 8.7 Hz, 2 H), 7.15 -7.31 (m, 9 H).	15	Similar to Exampl 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Exampl 49	45	1.74-1.84 (m, 2 H), 2.12-2.23 (m, 2 H), 2.37-2.45 (m, 2 H), 2.60-2.71 (m, 8 H), 3.02 (s, 3 H), 3.70 (s, 2 H), 4.03 (t, J = 7.6 Hz, 1 H), 6.85 (dt, J = 6.6, 1.5 Hz, 1 H), 6.94 (td, J = 10.2, 1.6 Hz, 1 H), 7.02 (d, J = 7.6 Hz, 1 H), 7.14-7.31(m, 6 H), 7.54 (d, J = 8.6 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	35	Similar to Example 1
Example 50	46	1.72-1.88 (m, 2 H), 2.15-2.30 (m, 2 H), 2.40-2.60 (m, 2 H), 2.60-2.90 (m, 8 H), 3.55 (s, 2 H), 3.78 (t, 1 H, J = 7.6 Hz), 6.53 (d, 2 H, J = 8.5 Hz), 6.98 (d, 2 H, J = 8.5 Hz), 7.1 - 7.3 (m, 9 H).	39	Similar to Example 16
Example 51	47	1.75-1.85 (m, 2 H), 2.12-2.21 (m, 2 H), 2.39-2.45 (m, 2 H), 2.65-2.77 (m, 8 H), 3.04 (s, 3 H), 3.70 (s, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 6.90-6.98 (m, 4 H), 7.12-7.26 (m, 4 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	36	Similar to Example 1
Example 52	48	1.75-1.85 (m, 2 H), 2.18-2.26 (m, 2 H), 2.42-2.52 (m, 2 H), 2.62-2.76 (m, 8 H), 3.04 (s, 3 H), 3.75 (s, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 6.91-6.99 (m, 2 H), 7.13-7.31 (m,, 7 H), 7.54 (d, J = 8.6 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	19	Similar to Example 1
Example 53	49	1.74-1.85 (m, 2 H), 2.17-2.28 (m, 2 H), 2.43-2.52 (m, 2 H), 2.63-2.72 (m, 8 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 4.38 (t, J = 7.6 Hz, 1 H), 6.94-7.21 (m, 4 H), 7.25-7.31 (m, 5 H), 7.54 (d, J = 8.6 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	45	Similar to Example 1
Example 54	50	1.72–1.85 (m, 2 H), 2.14–2.28 (m, 2 H), 2.44 (t, J = 7.3 Hz, 2 H), 2.60–2.76 (m, 8 H), 3.55 (s, 2 H), 4.00 (t, J = 7.7 Hz, 1 H), 7.10 –7.31 (m, 13 H).	14	Similar to Example 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synth tic method
Exampl 55	51	1.74–1-85 (m, 2 H), 2.15–2.25 (m, 2 H), 2.43–2.52 (m, 2 H), 2.60–2.75 (m, 8 H), 3.03 (s, 3 H), 3.71 (s, 2 H), 4.60 (t, J = 7.8 Hz, 1 H), 7.06–7.39 (m, 9 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	8	Similar t Example 1
Example 56	52	1.69–1-77 (m, 2 H), 2.15–2.30 (m, 2 H), 2.37–2.45 (m, 2 H), 2.60–2.69 (m, 8 H), 3.57 (s, 2 H), 4.00 (t, J = 7.7 Hz, 1 H), 6.97 (t, J_{H-F} = 8.9 Hz, 2 H), 7.11–7.18 (m, 2 H), 7.21–7.30 (m, 10 H).	21	Similar to Example 1
Example 57	53	1.71–1-79 (m, 2 H), 2.10–2.20 (m, 2 H), 2.33–2.40 (m, 2 H), 2.57–2.69 (m, 8 H), 3.57 (s, 2 H), 3.99 (t, J = 7.8 Hz, 1 H), 7.10–7.15 (m, 4 H), 7.20–7.25 (m, 8 H).	23	Similar to Example 1
Example 58	54	1.70–1-79 (m, 2 H), 2.11–2.17 (m, 2 H), 2.33–2.41 (m, 2 H), 2.60–2.68 (m, 8 H), 3.58 (s, 2 H), 4.00 (t, J = 7.7 Hz, 1 H), 6.90–6.99 (m, 4 H), 7.12–7.20 (m, 4 H), 7.26 (s, 4 H).	15	Similar to Example 1
Example 59	56	1.86–1-93 (m, 2 H), 2.25–2.37 (m, 2 H), 2.54–2.60 (m, 2 H), 2.67–2.95 (m, 8 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 4.00 (t, J = 7.9 Hz, 1 H), 7.11–7.19 (m, 4 H), 7.20–7.30 (m,, 4 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	10	Similar to Example 1
Example 60	57	1.73–1-86 (m, 2 H), 2.22–2.31 (m, 2 H), 2.43–2.52 (m, 2 H), 2.65–2.80 (m, 8 H), 3.55 (s, 2 H), 3.91 (t, J = 7.6 Hz, 1 H), 6.3 (broad s,1 H), 6.61 (d, J = 8.2 Hz, 2 H), 7.08–7.32 (m, 12 H).	29	Similar to Example 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 61	58	1.70-1.85 (m, 2 H), 2.15-2.28 (m, 2 H), 2.40-2.54 (m, 2 H), 2.57-2.80 (m, 8 H), 3.05 (S, 3 H), 3.69 (s, 2 H), 3.90 (t, J = 7.3 Hz, 1 H), 6.60-6.68 (m, 2 H), 6.80 (d, J = 7.9 Hz, 1 H), 7.08-7.32 (m, 6 H), 7.52 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	48	Similar to Example 1
Example 62	59	1.90-2.10 (m, 2 H), 2.40-2.97 (m, 12 H), 3.05 (S, 3 H), 3.75 (s, 2 H), 4.40-4.50 (m, 1 H), 6.65-6.77 (m, 2 H), 6.93 (d, J = 7.6 Hz, 1 H), 7.00-7.10 (m, 1 H), 7.15-7.35 (m, 5 H), 7.60 (d, J = 8.3 Hz, 2 H), 7.89 (d, J = 8.3 Hz, 2 H).	44	Similar to Example 1
Example 63	60	1.73-1-79 (m, 2 H), 2.15-2.26 (m, 2 H), 2.37-2.47 (m, 2 H), 2.60-2.75 (m, 8 H), 2.98 (broad s, 3 H), 3.10 (broad s, 3 H), 3.64 (s, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 7.15-7.33 (m, 10 H), 7.35 (s, 4 H).	29	Similar to Example 1
Example 64	61	1.70-1-76 (m, 2 H), 2.10-2.24 (m, 2 H), 2.35-2.45 (m, 2 H), 2.58-2.70 (m, 8 H), 3.64 (s, 2 H), 3.97 (t, J = 7.6 Hz, 1 H), 4.90 (broad s,2 H), 7.10-7.30 (m, 10 H), 7.42 (d, J = 8.1 Hz, 2 H) , 7.82 (d, J = 8.1 Hz, 2 H).	10	Similar to Example 1
Exampl 65	62	7.54 (d, J = 8.1Hz, 4 H), 7.34 (d, J = 8.1Hz, 4 H), 7.26 (s, 4 H), 4.20 (t, J = 7.6Hz, 1 H), 3.58 (s, 2 H), 2.69-2.61 (m, 8 H), 2.42-2.37 (m, 2 H), 2.25-2.17 (m, 2 H), 1.81-1.72 (m, 2 H).	72	Similar to Exampl 1
Example 66	63	1.65-1.80 (m, 2 H), 2.10-2.25 (m, 2 H), 2.40-2.51 (m, 2 H), 2.51-2.74 (m, 8 H), 3.53 (s, 2 H), 3.84 (t, J = 7.6 Hz, 1 H), 6.53 (s, 1 H), 6.60 (dd, J = 1.6, 7.9 Hz, 1 H), 6.76 (d, J = 7.6 Hz, 1 H), 7.06-7.33 (m, 10 H).	19	Similar to Example 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Exampl 67	64	1.85-2.10 (m, 2 H), 2.30-2.90 (m, 12 H), 3.61 (s, 2 H), 4.40-4.50 (m, 1 H), 6.64-6.75 (m, 2 H), 6.93 (d, J = 7.9 Hz, 1 H), 7.00-7.10 (m, 1 H), 7.15-7.40 (m, 9 H).	39	Similar to Example 1
Example 68	65	1.72-1.81 (m, 2 H), 2.10-2.19 (m, 2 H), 2.42-2.45 (m, 2 H), 2.64-2.72 (m, 8 H), 3.58 (s, 2 H), 3.76 (s, 6 H), 6.80 (d, 4 H, J = 8.91 Hz), 7.13 (d, 4 H, J = 8.91 Hz), 7.26 (s, 4 H).	49	Similar to Example 1
Example 69	66	1.83-1.85 (m, 2 H), 2.16-2.24 (m, 2 H), 2.59-2.72 (m, 6 H), 2.84-2.94 (m, 4 H), 3.62 (s, 2 H), 3.76 (m, 1 H), 6.69 (d, 4 H, J = 8.58 Hz), 7.05 (d, 4 H, J = 8.58 Hz), 7.30 (s, 4 H).	19	Similar to Example 1
Example 70	67	1.81-1.85 (m, 2 H), 2.15-2.24 (m, 2 H), 2.56-2.62 (m, 2 H), 2.68-2.72 (m, 4 H), 2.81-2.91 (m, 4 H), 3.10 (s, 3 H), 3.73-3.78 (m, 3 H), 6.68 (d, 4 H, J = 8.58 Hz), 7.05 (d, 4 H, J = 8.58 Hz), 7.59 (d, 2 H, J = 8.58 Hz), 7.89 (d, 2 H, J = 8.58 Hz).	3	Similar to Exampl 1
Example 71	68	1.74–1.80 (m, 2 H), 1.90 (broad s, 2 H), 2.12–2.28 (m, 2 H), 2.40–2.76 (m, 10 H), 2.91 (s, 3 H), 3.49 (s, 2 H), 6.84–6.88 (m, 1 H), 7.00–7.20 (m, 6 H), 7.30–7.35 (m, 2 H), 7.43 (d, J = 8.4 Hz, 2 H), 7.74 (d, J = 8.4 Hz, 2 H).	1	Similar to Example 1
Exampl 72	102	1.38-1.52 (m, 2 H), 1.72-1.86 (m, 2 H), 1.98-2.12 (m, 2 H), 2.52 (t, J = 7.6 Hz, 2 H), 2.58-2.75 (m, 8 H), 3.05 (S, 3 H), 3.69 (s, 2 H), 3.89 (t, J = 7.9 Hz, 1 H), 7.11-7.31 (m, 10 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H).	59	Similar to Example 1

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic m thod
Example 73	103	1.71–1.77 (m, 2 H), 2.33–2.39 (m, 2 H), 2.49–2.55 (m, 2 H), 2.57–2.71 (m, 8 H), 3.05 (s, 3 H), 3.07 (s, 3 H), 3.67 (s, 2 H), 7.15–7.36 (m, 10 H), 7.52 (d, J = 8.3 Hz, 4 H), 7.86 (d, J = 8.3 Hz, 2 H).	4	Similar to Exampl 1
Example 74	104	1.63–1.80(m, 2 H), 2.10–2.20 (m, 2 H), 2.35–2.75 (m, 13 H), 3.01 (s, 3 H), 3.05 (s, 3 H), 3.61 (s, 2 H), 6.55–6.67 (m, 4 H), 6.80–6.90 (m, 2 H), 7.03–7.13 (m, 2 H), 7.46 (d, J = 8.1 Hz, 2 H), 7.84 (d, J = 8.1 Hz, 2 H).	20	Similar to Example 1
Example 75	106	1.79-1.88 (m, 2 H), 2.37-2.41 (m, 2 H), 2.56-2.71 (m, 10 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 7.15-7.20 (m, 2 H), 7.26-7.32 (m, 4 H), 7.45-7.48 (m, 4H), 7.56 (d, 2 H, J = 8.25 Hz), 7.88 (d, 2 H, J = 8.58 Hz).	69	Similar t Example 9
Example 76	108	1.75-1.86 (m, 2 H), 2.29 (s, 6 H), 2.32-2.36 (m, 2 H), 2.53-2.71 (m, 10 H), 3.57 (s, 2 H), 7.09 (d, 2 H, J = 8.24 Hz), 7.26 (s, 4 H), 7.33 (d, 2 H, J = 8.25 Hz).	26	Similar to Exampl 9
Example 77	109	1.57–1-61 (m, 2 H), 2.12–2.24 (m, 2 H), 2.32–2.57 (m, 10 H), 3.45 (s, 2 H), 4.75 (broad s, 3 H), 6.40–6.51 (m,2 H), 6.67–6.77 (m,4 H), 6.88–7.00 (m,2 H), 7.09–7.20 (m, 4 H). (solvent: CD_3OD)	75	Similar to Example 12
Example 78	110	1.80-1.84 (m, 2 H), 2.38-2.42 (m, 2 H), 2.58-2.72 (m, 10 H), 3.58 (s, 2 H), 7.27 (s, 4 H), 7.54-7.62 (m, 8 H).	84	Similar to Example 9

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic meth d
Example 79	111	7.35 (d, J = 8.9Hz, 4 H), 7.26 (s, 4 H), 6.82 (d, J = 8.9Hz, 4 H), 3.76 (s, 6H), 3.56 (s, 2 H), 2.70-2.53 (m, 10 H), 2.33-2.29 (m, 2 H), 1.83-1.78 (m, 2 H).	38	Similar to Example 9
Example 80	112	7.26 (s, 4 H), 7.26-7.70 (m, 6 H), 6.36 (dd, J = 7.9, 2.0Hz, 2 H), 3.77 (s, 6 H), 3.57 (s, 2 H), 2.71-2.55 (m, 10 H), 2.36-2.32 (m, 2 H), 1.83-1.79 (m, 2 H).	22	Similar to Example 9
Example 81	113	1.84-1.88 (m, 2 H), 2.46-2.48 (m, 2 H), 2.66-2.76 (m, 10 H), 3.04 (s, 3 H), 3.72 (s, 2 H), 7.25-7.43 (m, 6 H), 7.56-7.60 (m, 10 H), 7.88 (d, 2 H, J = 8.58 Hz).	89	Similar to Example 9
Example 82	114	1.65–1.78 (m, 2 H), 2.27–2.38 (m, 2 H), 2.45–2.68 (m, 11 H), 3.04 (s, 3 H), 3.59 (s, 2 H), 6.62 (d, J = 7.9 Hz, 2 H), 6.90–7.13 (m, 6 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H).	52	Similar to Example 12
Example 83	115	7.87 (d, J = 8.2Hz, 2 H), 7.66 (d, J = 7.6Hz, 2 H), 7.54 (d, J = 8.2Hz, 2 H), 7.18 (t, J = 7.6Hz, 2 H), 6.97 (t, J = 7.6Hz, 2 H), 6.78 (d, J = 7.7Hz, 2H), 3.69 (s, 2 H), 3.42 (s,6 H), 3.05 (s, 3 H), 2.78-2.50 (m, 12 H), 1.86-1.81 (m, 2 H).	83	Similar to Example 9
Exampl 84	116	1.28 (s, 18 H), 1.84-1.86 (m, 2 H), 2.34-2.38 (m, 2 H), 2.54-2.72 (m, 10 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 7.27-7.31 (m, 4 H), 7.36-7.39 (m, 4 H), 7.56 (d, 2 H, J = 8.58 Hz), 7.88 (d, 2 H, J = 8.25 Hz).	83	Similar to Example 9

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Exampl 85	117	7.89 (d, J = 8.3Hz, 2 H), 7.58-7.54 (m, 10 H), 3.72 (s, 2 H), 3.05 (s, 3 H), 2.72-2.59 (m, 10 H), 2.43-2.39 (m, 2 H), 1.84-1.80 (m, 2 H), 1.59 (br s, 1 H).	61	Similar to Exampl 9
Example 86	118	1.80–1.90 (m, 2 H), 1.85 (s, 6 H), 2.45–2.52 (m, 4 H), 2.65–2.80 (m, 8 H), 3.05 (s, 3 H), 3.10 (broad s, 1 H), 3.72 (s, 2 H), 7.01 (d, J = 7.4 Hz, 2 H), 7.13 (t, J = 7.4 Hz, 2 H), 7.20 (t, J = 7.4 Hz, 2 H), 7.56 (d, J = 8.1 Hz, 2 H), 7.77 (d, J = 7.8 Hz, 2 H), 7.88 (d, J = 8.1 Hz, 2 H). (solvent: $CDCl_3$-CD_3OD)	13	Similar to Example 9
Example 87	120	1.85–1.97 (m, 2 H), 2.39–2.49 (m, 4 H), 2.67–2.85 (m, 9 H), 2.85–2.95 (m, 2 H), 3.04 (s, 3 H), 3.71 (s, 2 H), 7.05–7.15 (m, 2 H), 7.18–7.27 (m, 2 H), 7.53–7.62 (m, 4 H), 7.67–7.80 (m, 4 H), 7.88 (d, J = 8.3 Hz, 2 H), 8.17 –8.31 (m, 4 H).	10	Similar to Example 9
Example 88	121	1.75–1.89 (m, 2 H), 2.28–2.33 (m, 2 H), 2.51–2.57 (m, 2 H), 2.58–2.75 (m, 9 H), 2.89 (s, 12 H), 3.04 (s, 3 H), 3.70 (s, 2 H), 6.67 (d, J = 8.6 Hz, 4 H), 7.29 (d, J = 8.6 Hz, 4 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 8.3 Hz, 2 H).	33	Similar t Exampl 9
Example 89	122	1.81-1.86 (m, 2 H), 2.26-2.30 (m, 2 H), 2.58-2.73 (m, 10 H), 3.06 (s, 3 H), 3.71 (s, 2 H), 5.91 (s, 4 H), 6.72-6.75 (m, 2 H), 6.91-6.94 (m, 4 H), 7.56 (d, 2 H, J = 8.25 Hz), 7.88 (d, 2 H, J = 8.25 Hz).	84	Similar to Exampl 9
Example 90	123	1.73–1.81(m, 2 H), 2.26–2.31 (m, 2 H), 2.48–2.46 (m, 2 H), 2.56–2.78 (m, 8 H), 3.54 (s, 2 H), 4.40 (broad s, 3 H), 6.72 (d, J = 8.6 Hz, 4 H), 7.20 (d, J = 8.6 Hz, 2 H), 7.23–7.25 (m, 4 H). (solvent: $CDCl_3$-CD_3OD)	36	Similar to Example 12

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synth tic meth d
Example 91	125	7.88 (d, J = 8.3Hz, 2 H), 7.63-7.55 (m, 3 H), 7.40-7.04 (m, 8 H), 6.60 (s, 1H), 3.73 (s, 2 H), 3.44 (s, 3 H), 3.05 (s, 3 H), 2.88-2.55 (m, 11 H), 2.80-2.11 (m, 1H), 1.92-1.85 (m, 2 H).	24	Similar to Example 14
Example 92	126	1.78-1.91 (m, 2 H), 2.33-2.41 (m, 2 H), 2.62-2.80 (m, 10 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 6.91-6.98 (m, 4 H), 7.19 (dd, J = 3.3, 3.3 Hz, 2 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.88 (d, J = 8.6 Hz, 2 H).	74	Similar to Example 9
Exampl 93	128	1.78-1.91 (m, 2 H), 2.25-2.35 (m, 2 H), 2.55-2.78 (m, 10 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 7.00 (dd, J = 3.3, 3.3 Hz, 2 H) , 7.20-7.30 (m, 4 H), 7.56 (d, J = 8.6 Hz, 2 H), 7.88 (d, J = 8.6 Hz, 2 H).	19	Similar to Exampl 11
Example 94	130	1.80-1.96 (m, 2 H), 1.91 (s, 6 H), 2.45-2.53 (m, 2 H), 2.63-2.77 (m, 8 H), 2.81 (t, J = 5.6 Hz, 2 H), 3.06 (s, 3 H), 3.71 (s, 2 H), 6.77 (d, J = 5.3 Hz, 2 H), 7.06 (d, J = 5.3 Hz, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H).	23	Similar to Example 9
Example 95	131	7.88 (d, J = 8.3Hz, 2 H), 7.54 (d, J = 8.3Hz, 2 H), 7.45 (d, J = 6.9Hz, 2 H), 7.31-7.13 (m, 4 H), 7.03-6.96 (m, 2 H), 6.68-6.65 (m, 1 H), 3.69 (s, 2 H), 3.05 (s, 3 H), 2.74-2.58 (m, 10 H), 1.8 (br s, 1 H), 2.39-2.35 (m, 2 H), 1.85-1.81 (m, 2 H).	8	Similar to Example 15
Example 96	132	1.77–1.88 (m, 2 H), 2.35–2.38 (m, 2 H), 2.49–2.58 (m, 2 H), 2.58–2.87 (m, 10H), 3.05 (s, 3H), 3.68 (s, 2H), 3.77 (t, J = 7.6 Hz, 1 H), 6.58–6.72 (m, 6 H), 7.03–7.12 (m, 6 H), 7.50 (d, J = 8.3 Hz, 2 H), 7.86 (d, J = 8.3 Hz, 2 H).	30	Similar to Example 15

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synth tic m thod
Example 97	133	1.79–1.89 (m, 2 H), 2.35–2.40 (m, 2 H), 2.55–2.76 (m, 11 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 3.77 (s, 3 H), 6.70–6.75 (m, 1 H), 6.99–7.03 (m, 1 H), 7.13–7.31 (m, 4 H), 7.45–7.49 (m, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 2 H).	30	Similar to Example 15
Example 98	134	1.66–1.75 (m, 2 H), 2.17 (s, 3 H), 2.19–2.26 (m, 2 H), 2.40–2.76 (m, 11 H), 2.91 (s, 3 H), 3.49 (s, 2 H), 6.84–6.88 (m, 1 H), 7.00–7.20 (m, 6 H), 7.30–7.35 (m, 2 H), 7.43 (d, J = 8.4 Hz, 2 H), 7.74 (d, J = 8.4 Hz, 2 H).	21	Similar to Exampl 15
Example 99	135	1.79–1.88 (m, 2 H), 2.35–2.41 (m, 2 H), 2.54–2.78 (m, 11 H), 3.03 (s, 3 H), 3.70 (s, 2 H), 7.10–7.48 (m, 8 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 8.3 Hz, 2 H).	11	Similar to Exampl 15
Example 100	136	1.77–1.88 (m, 2 H), 2.35–2.40 (m, 2 H), 2.55–2.76 (m, 11 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 3.77 (s, 3 H), 6.70–6.75 (m, 1 H), 6.99–7.03 (m, 1 H), 7.13–7.31 (m, 4 H), 7.45–7.49 (m, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 2 H).	7	Similar to Example 15
Example 101	137	7.86 (d, J = 8.3Hz, 2 H), 7.52 (d, J = 8.3Hz, 2 H), 7.42-7.37 (m, 2 H), 7.15 (t, J = 7.9Hz, 1 H), 7.07-6.89 (m, 7 H), 6.69-6.65-6.47 (m, 1 H), 3.65 (s, 2H), 3.05 (s, 3 H), 2.75-2.59 (m, 10 H), 2.39-2.32 (m, 2 H), 1.85-1.74 (m, 2 H).	12	Similar to Example 15
Example 102	139	7.87 (d, J = 8.3 Hz, 2 H), 7.60-6.94 (m, 9 H), 6.67-6.63 (m, 1 H), 5.75 (s, 1 H), 4.11-3.97 (m, 4 H), 3.68 (s, 2 H), 3.05 (s, 3 H), 2.85-2.58 (m, 10 H), 2.42-2.33 (m, 2 H), 1.88-1.72 (m, 2 H).	6	Similar to Exampl 15

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 103	140	1.65–1.78 (m, 2 H), 2.20–2.29 (m, 2 H), 2.41–2.61 (m, 10 H), 2.77 (s, 3 H), 2.90 (s, 3 H), 3.57 (s, 2 H), 3.72–3.79 (m, 2 H), 4.91–5.04 (m, 2 H), 5.59–5.75 (m, 1 H), 6.39–6.44 (m, 1 H), 6.55–6.62 (m, 1 H), 6.80–6.83 (m, 1 H), 6.96–7.08 (m, 3 H), 7.10–7.18 (m, 2 H), 7.30–7.39 (m, 2 H), 7.43 (d, J = 8.2 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H).	17	Similar to Example 15
Example 104	141	1.75–1.89(m, 2 H), 2.35–2.48 (m, 2 H), 2.48–2.85 (m, 11 H), 3.03 (s, 3 H), 3.46 (s, 3 H), 3.68 (s, 2 H), 3.78 (s, 3 H), 6.36 (d, J = 2.3 Hz, 1 H), 6.53 (dd, J = 8.6, 2.3 Hz, 1 H), 7.09–7.17 (m, 1H), 7.18–7.31 (m, 2 H), 7.35–7.45 (m, 2 H), 7.55 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 8.1 Hz, 2 H).	28	Similar to Example 15
Exampl 105	142	1.75–1.89(m, 2 H), 2.31–2.38 (m, 2 H), 2.54–2.74 (m, 11 H), 3.04 (s, 3 H), 3.70 (s, 2 H), 3.75 (s, 6 H), 6.30 (t, J = 2.2 Hz, 1 H), 6.66 (d, J = 2.2 Hz, 2 H), 7.13–7.20 (m, 1 H), 7.22–7.32 (m, 2H), 7.46 (d, J = 8.4 Hz, 2 H), 7.55 (d, J = 8.4 Hz, 2 H).	25	Similar t Exampl 15
Example 106	143	1.65–1.78(m, 2 H), 2.20–2.29 (m, 2 H), 2.41–2.61 (m, 10 H), 2.77 (s, 3 H), 2.90 (s, 3 H), 3.57 (s, 2 H), 3.72–3.79 (m, 2 H), 4.91–5.04 (m, 2 H), 5.59–5.75 (m, 1 H), 6.39–6.44 (m, 1 H), 6.55–6.62 (m, 1 H), 6.80–6.83 (m, 1 H), 6.96–7.08 (m, 3 H), 7.10–7.18 (m, 2 H), 7.30–7.39 (m, 2 H), 7.43 (d, J = 8.2 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H).	17	Similar to Example 15
Example 107	144	1.78-1.82 (m, 2 H), 2.19-2.27 (m, 2 H), 2.43-2.48 (m, 2 H), 2.67-2.82 (m, 6 H), 3.40-3.45 (m, 1 H), 3.76 (s, 2 H), 3.99-4.05 (m, 2 H), 7.14-7.30 (m, 10 H), 7.65 (d, 2 H, J = 8.25 Hz), 7.96 (d, 2 H, J = 8.25 Hz).	21	Similar to Exampl 1
Example 108	145	7.87 (d, J = 8.2 Hz, 2 H), 7.54 (d, J = 8.2 Hz, 2 H), 7.36-6.94 (m, 7 H), 6.68-6.64 (m, 1 H), 3.79 (t, J = 6.4 Hz, 2 H), 3.67 (s, 2 H), 3.05 (s, 3 H), 2.81 (t, J = 6.4 Hz, 2 H), 2.71-2.58 (m, 10 H), 2.44-2.33 (m, 2 H), 1.87-1.82 (m, 2 H).	10	Similar to Example 15

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic m thod
Example 109	147	1.79–1.90 (m, 2 H), 2.30–2.41 (m, 2 H), 2.58–2.79 (m, 11 H), 3.04 (s, 3 H), 3.66 (s, 2 H), 6.65–6.71 (m, 1 H), 6.85–7.00 (m, 5 H), 7.02–7.20 (m, 3 H), 7.25–7.35 (m, 2 H), 7.35–7.45 (m, 2 H), 7.52 (d, J = 8.3 Hz, 2 H), 7.86 (d, J = 8.3 Hz, 2 H).	26	Similar to Example 15
Example 110	148	1.78–1.90 (m, 2 H), 2.30–2.40 (m, 2 H), 2.53–2.79 (m, 11 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 3.83 (s, 3 H), 5.50 (broad s, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.90 (dd, J = 8.3 Hz, 2.0 Hz, 1 H), 7.04 (d, J = 2.0 Hz, 1 H), 7.14–7.22 (m, 1 H), 7.24–7.37 (m, 2 H), 7.40–7.50 (m, 2 H), 7.56 (d, J = 8.2 Hz, 2 H), 7.88 (d, J = 8.2 Hz, 2 H).	24	Similar to Example 15
Example 111	149	1.77–1.90 (m, 2 H), 2.28–2.38 (m, 2 H), 2.50–2.73 (m, 12 H), 3.05 (s, 3 H), 3.69 (s, 2 H), 3.74 (s, 3 H), 6.23–6.26 (m, 1 H), 6.55–6.58 (m, 1 H), 6.61–6.64 (m, 1 H), 7.14–7.20 (m, 1 H), 7.22–7.33 (m, 2 H), 7.42–7.49 (m, 2 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H).	12	Similar to Example 15
Example 112	150	7.88 (d, J = 8.3 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.47 (d, J = 7.9 Hz, 2 H), 7.30-7.09 (m,7 H), 7.07 (s, 1 H), 6.90-6.71 (m, 1 H), 5.88-5.75 (m, 2 H), 5.16-5.08 (m, 4 H), 3.95-3.80 (m, 4 H), 3.70 (s, 2 H), 3.05 (s, 3 H), 2.71-2.56 (m, 10 H), 2.37-2.33(m, 2 H), 1.88-1.77 (m, 2 H).	67	Similar to Example 15
Example 113	151	1.82-1.86 (m, 2 H), 2.37-2.41 (m, 2 H), 2.57-2.73 (m, 10 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 4.64 (s, 2 H), 7.15-7.21 (m, 4 H), 7.26-7.32 (m, 4 H), 7.56 (d, 2 H, J = 8.25 Hz), 7.88 (d, 2 H, J = 8.25 Hz).	33	Similar t Exampl 15
Example 114	152	7.89 (d, J = 8.6 Hz, 2 H), 7.56 (d, J = 8.6 Hz, 2 H), 7.38-7.16 (m, 8 H), 7.07 (s, 1 H), 4.39 (d, J = 11.8 Hz, 1 H), 4.01 (d, J = 11.8Hz, 1 H), 3.72 (s, 2 H), 3.06 (d, J = 13.3 Hz, 1H) 2.90-2.45 (m, 11 H), 2.33-2.14 (m, 1 H), 1.90-1.77 (m, 2 H).	2	Similar t Example 15 (a)

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 115	153	7.89 (d, J = 8.3 Hz, 4 H), 7.76-7.72 (m, 2 H), 7.57 (d, J = 8.3 Hz, 2 H), 7.36-7.19 (m, 3 H), 3.72 (s, 2 H), 3.04 (s, 3 H), 2.82-2.56 (m, 11 H), 2.39-2.30 (m, 1 H), 1.89-1.81 (m, 2 H).	24	Similar to Example 14
Example 116	154	1.80-1.84 (m, 2 H), 2.04 (m, 2 H), 2.59-2.69 (m, 10 H), 3.04 (s, 3 H), 3.67 (s, 2 H), 3.89 (s, 3 H), 6.64-6.67 (m, 1 H), 7.00-7.19 (m, 5 H), 7.41-7.44 (m, 1 H), 7.53 (d, 2 H, J = 7.25 Hz), 7.61-7.72 (m, 2 H), 7.85-7.91 (m, 3 H).	58	Similar to Example 15
Example 117	155	0.84-0.89 (m, 3 H), 1.23-1.37 (m, 12 H), 1.55-1.58 (m, 2 H), 1.78-1.79 (m, 2 H), 2.33 (m, 1 H), 2.50-2.76 (m, 12 H), 3.04 (s, 3 H), 3.65 (s, 2 H), 6.63-6.67 (m, 1 H), 6.95 (d, 1 H, J = 7.59 Hz), 7.06-7.17 (m, 4 H), 7.33 (d, 2 H, J = 8.25 Hz), 7.52 (d, 2 H, J = 8.25 Hz), 7.86 (d, 2 H, J = 8.58 Hz).	51	Similar t Example 15
Exampl 118	156	8.48 (br s, 1 H), 7.72 (d, J = 8.3 Hz, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 7.50-7.47 (m, 2 H), 7.33-7.17 (m, 3 H), 6.68-6.66 (m, 1 H), 6.17-6.06 (m, 2 H), 3.71 (s, 2 H), 3.05 (s, 3 H), 3.03 (d, J = 13.3 Hz, 1 H), 2.80-2.50 (m, 10 H), 2.39-2.28 (m, 1 H), 2.13-2.13 9m, 1 H), 1.88-1.79(m, 2 H).	16	Similar to Example 14 ....(a)
Example 119	157	7.89 (d, J = 8.3 Hz, 2 H), 7.66-7.62 (m, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 7.34-7.18 (m, 3 H), 7.00 (s, 2 H), 3.71 (s, 2 H), 3.04 (s, 3 H), 3.06 (d, J = 13.3 Hz, 1 H), 2.79-2.51 (m, 11 H), 2.30-2.17 (m, 1 H), 1.87-1.78 (m, 2 H).	21	Similar to Example 14 ....(a)
Example 120	158	1.73–1.83 (m, 2 H), 2.26–2.44 (m, 2 H), 2.45–2.75 (m, 11 H), 3.05 (s, 3 H), 3.62 (s, 2 H), 6.60–6.68 (m, 1 H), 6.88–6.95 (m, 1 H), 7.00–7.02 (m, 1 H), 7.07–7.15 (m, 1 H), 7.31–7.58 (m, 5 H), 7.78–7.88 (m, 3 H).	31	Similar to Example 15

(a) 2-(Trimethylsilyl)ethoxymethyl group was used as protective group.

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synth tic method
Example 121	159	7.88 (d, J = 8.3 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.32-7.05 (m, 4 H), 6.84-6.82 (m, 2 H), 6.54-6.50 (m, 1 H), 3.71 (s, 2 H), 3.05 (s, 3 H), 3.03 (d, J = 13.3 Hz, 1 H), 2.86-2.53 (m, 10 H), 2.46-2.33 (m, 2 H), 1.90-1.77 (m, 2 H).	39	Similar to Example 17
Example 122	160	7.88 (d, J = 8.3 Hz, 2 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.46 (d, J = 7.3 Hz, 2 H), 7.33-7.17 (m, 3 H), 6.69-6.66 (m, 1 H), 6.17-6.07 (m, 2 H), 3.97 (d, J = 5.3 Hz, 2 H), 3.74 (s, 2 H), 3.33 (d, J = 5.3 Hz, 2 H), 2.79-2.50 (m, 10 H), 2.38-2.14 (m, 2 H), 1.89-1.80 (m, 2 H).	12	Similar to Example 14 (a), (b)
Example 123	161	1.76 - 1.78 (m, 2 H), 2.31 (m, 2 H), 2.60 - 2.67 (m, 10 H), 3.02 (s, 3 H), 3.61 (s, 2 H), 5.75 (s, 1 H), 6.62 - 6.65 (m, 1 H), 6.90 - 6.93 (m, 1 H), 7.03 (s, 1 H), 7.09 - 7.15 (m, 1 H), 7.23 - 7.39 (m, 9 H), 7.49 (d, 2 H, J = 8.25 Hz), 7.83 (d, 2 H, J = 8.25 Hz).	50	Similar to Exampl 15
Exampl 124	163	The structure was confirmed by ESI/MS *m/e* 515.5 (M^++H, $C_{28}H_{32}F_2N_2O_3S$).	12	Similar to Example 9
Example 125	164	1.77−1.90 (m, 2 H), 2.29−2.38 (m, 2 H), 2.53−2.80 (m, 10 H), 3.05 (s, 3 H), 3.71 (s, 2 H), 6.35 (broad s, 1 H), 6.90−7.05 (m, 4 H), 7.35−7.45 (m, 4 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H).	9	Similar t Example 9
Example 126	165	The structure was confirmed by ESI/MS *m/e* 547.5 (M^++H, $C_{28}H_{32}Cl_2N_2O_3S$).	10	Similar to Example 9

(a) 2-(Trimethylsilyl)ethoxymethyl group was used as protective group.

(b) Compound No.160 was obtained as the by-product in preparation of compound No.156.

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 127	166	The structure was confirmed by ESI/MS *m/e* 547.5 (M^++H, $C_{28}H_{32}Cl_2N_2O_3S$).	6	Similar t Exampl 9
Example 128	167	1.78−1.89 (m, 2 H), 2.30−2.38 (m, 2 H), 2.54−2.76 (m, 11 H), 3.05 (s, 3 H), 3.70 (s, 2 H), 3.77 (s, 6 H), 6.69−6.75 (m, 2 H), 6.97−7.03 (m, 2 H), 7.07−7.10 (m, 2 H), 7.16−7.24 (m, 2 H), 7.55 (d, J = 8.3 Hz, 2 H) , 7.88 (d, J = 8.3 Hz, 2 H).	12	Similar to Example 9
Example 129	168	The structure was confirmed by ESI/MS *m/e* 539.5 (M^++H, $C_{30}H_{38}N_2O_3S$).	67	Similar t Exampl 12
Example 130	169	1.76-1.92 (m, 2 H), 2.28-2.40 (m, 2 H), 2.52-2.77 (m, 10 H), 3.06 (s, 3 H), 3.70 (s, 2 H), 6.68 (dd, J = 7.9 and 1.7 Hz, 1 H), 6.82-6.93 (m, 1 H), 6.95-7.03 (m, 2 H), 7.13-7.31 (m, 4 H), 7.55 (d, J = 8.6 Hz, 2 H), 7.88 (d, J = 8.6 Hz, 2 H).	52	Similar to Example 15
Example 131	170	1.77-1.90 (m, 2 H), 2.25-2.39 (m, 2 H), 2.52-2.78 (m, 10 H), 3.06 (s, 3 H), 3.70 (s, 2 H), 6.68 (dd, J = 7.9 and 2.3 Hz, 1 H), 6.92-7.02 (m, 2 H), 7.12-7.35 (m, 4 H), 7.49 (s, 1 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H).	62	Similar to Exampl 15
Example 132	171	1.75-1.89 (m, 2 H), 2.28-2.40 (m, 2 H), 2.51-2.75 (m, 10 H), 3.05 (s, 3 H), 3.69 (s, 2 H), 6.67 (dd, J = 7.9 and 2.3 Hz, 1 H), 6.94 (d, J = 8.25 Hz, 1 H), 6.99 (d, J = 2.3 Hz, 1 H), 7.16 (dd, J = 7.9 and 7.9 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 2 H), 7.39 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 8.3 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H).	60	Similar to Example 15

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 133	172	1.70 − 1.81 (m, 2H), 2.25 − 2.34 (m, 2H), 2.50 − 2.72 (m, 12H), 3.03 (s, 3H), 3.60 (s, 2H), 3.69 (s, 6H), 6.23 − 6.27 (m, 1H), 6.59 − 6.68 (m, 3H), 6.88 − 6.95 (m, 1H), 7.07 − 7.17 (m, 2H), 7.48 (d, *J* = 8.3 Hz, 2H) , 7.83 (d, *J* = 8.3 Hz, 2H).	22	Similar to Example 15
Example 134	173	1.70 − 1.81 (m, 2H), 2.26 − 2.37 (m, 2H), 2.50 − 2.70 (m, 12H), 3.03 (s, 3H), 3.60 (s, 2H), 3.72 (s, 3H), 6.60 − 6.72 (m, 2H), 6.90 − 6.95 (m, 1H), 6.95 − 7.00 (m, 1H), 7.01 − 7.19 (m, 4H), 7.48 (d, *J* = 8.3 Hz, 2H) , 7.83 (d, *J* = 8.3 Hz, 2H).	33	Similar to Example 15
Example 135	197	7.88 (d, J = 8.3Hz, 2 H), 7.56 (d, J = 8.3Hz, 2 H), 7.51-7.47 (m, 4 H), 7.30-7.13 (m, 6 H), 3.71 (s, 2 H), 3.05 (s, 3 H), 2.73-2.46 (m, 8 H), 1.85-1.76 (m, 4 H), 1.62-1.59 (m, 2 H).	41	Similar t Example 9
Example 136	198	7.83 (d, J = 8.3Hz, 2 H), 7.43 (d, J = 8.4Hz, 2 H), 7.17-7.07 (m, 4 H), 6.91 (d, J =7.6Hz, 2 H), 3.56 (s, 2 H), 3.04 (s, 3 H), 2.62-2.42 (m, 12 H), 1.8 (br s), 1.75-1.50 (m, 4 H).	11	Similar to Example 12
Example 137	200	1.74-1.84 (m, 2 H), 2.11-2.21 (m, 2 H), 2.36-2.43 (m, 2 H), 2.59-2.67 (m, 4 H), 3.31-3.37 (m, 4 H), 3.97 (t, J = 7.6 Hz, 1 H), 7.12-7.30 (m, 10 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.72 (d, J = 8.6 Hz, 2 H).	70	Similar to Example 3
Example 138	201	1.69-1.79 (m, 1 H), 1.89-1.99 (m, 1 H), 2.13-2.28 (m, 2 H), 2.37-2.49 (m, 2 H), 2.54-2.62 (m, 2 H), 2.64-2.69 (m, 1 H), 2.75-2.80 (m, 1 H), 3.33-3.39 (m, 2 H), 3.73-3.78 (m, 2 H), 4.01 (dd, J = 17.5, 7.6 Hz, 1 H), 7.13-7.32 (m, 12 H), 8.63-8.69 (m, 2 H).	57	Similar to Example 3

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synth tic m thod
Example 139	203	1.70-1.85 (m, 2 H), 2.14-2.25 (m, 2 H), 2.30 (d, J = 2.0 Hz, 3 H), 2.34-2.45 (m, 2 H), 2.49-2.57 (m, 2 H), 2.60-2.68 (m, 2 H), 3.15 (d, J = 7.9 Hz, 2 H), 3.48-3.60 (m, 6 H), 3.99 (dt, J = 2.0, 7.6 Hz, 1 H), 7.12-7.32 (m, 15 H).	38	Similar to Example 4
Example 140	205	0.87 (t, J = 7.3 Hz, 3 H), 1.40-1.55 (m, 2 H), 1.71-1.81 (m, 2 H), 2.16-2.25 (m, 2 H), 2.37-2.45 (m, 4 H), 2.52-2.71 (m, 8 H), 4.00 (t, J = 7.9 Hz, 1 H), 7.12-7.20 (m, 2 H), 7.20-7.31 (m, 8 H).	25	Similar to Exampl 5
Example 141	208	1.74-1.83 (m, 2 H), 2.17-2.26 (m, 2 H), 2.40-2.47 (m, 2 H), 2.63-2.75 (m, 8 H), 3.44 (s, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 5.51 (s, 1 H), 7.13-7.32 (m, 10 H).	30	Similar to Example 6
Exampl 142	209	1.72-1.81 (m, 2 H), 2.17-2.27 (m, 2 H), 2.39-2.49 (m, 2 H), 2.47 (t, J = 7.6 Hz, 2 H), 2.63-2.73 (m, 8 H), 2.84 (t, J = 7.6 Hz, 2 H), 3.67 (s, 3 H), 3.99 (t, J = 7.6 Hz, 1 H), 7.12-7.20 (m, 2 H), 7.22-7.31 (m, 8 H).	64	Similar to Example 1
Example 143	235	2.17-2.35 (m, 4 H), 2.35-2.60 (m, 8 H), 3.50 (s, 2 H), 3.97 (t, J = 7.3 Hz, 1 H), 7.11-7.35 (m, 12 H), 8.53 (d, J = 5.9 Hz, 2 H).	17	Similar to Exampl 8
Exampl 144	238	1.77-1.86 (m, 2 H), 2.18-2.27 (m, 2 H), 2.40-2.46 (m, 2 H), 2.66-2.72 (m, 4 H), 2.78-2.88 (m, 6 H), 2.91-2.98 (m, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 6.97 (s, 1 H), 7.01-7.31 (m, 12 H), 7.35 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 7.9 Hz, 1 H), 7.94 (br, 1 H).	11	Similar to Example 5

Table 2 (continued)

	Compound No.	^{1}H NMR Data ($CDCl_3$) δ (ppm)	Yield (%)	Synthetic method
Example 145	239	1.68-1.78 (m, 2H), 2.14-2.24 (m, 2H), 2.24 (s, 3H), 2.32 (s, 3H), 2.36-2.43 (m, 2H), 2.53-2.67 (m, 8H), 3.30 (s, 2H), 4.00 (t, J = 7.6 Hz, 1H), 7.12-7.19 (m, 2H), 7.21-7.56 (m, 8H).	28	Similar to Example 7
Example 146	240	1.75-1.82 (m, 2H), 2.19-2.26 (m, 2H), 2.43-2.47 (m, 2H), 2.65-2.73 (m, 8H), 3.63 (s, 2H), 4.01 (t, J = 7.8 Hz, 1H), 7.14-7.19 (m, 2H), 7.23-7.29 (m, 10H), 8.52 (d, J = 5.9 Hz, 2H).	50	Similar to Example 1
Example 147	241	1.74-1.83 (m, 2 H), 2.18-2.27 (m, 2 H), 2.42-2.48 (m, 2 H), 2.66-2.74 (m, 8 H), 3.63 (s, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 7.12-7.30 (m, 11 H), 7.66 (ddd, J = 7.9, 2.0, 1.7 Hz, 1 H), 8.49 (dd, J = 4.6, 1.7 Hz, 1 H), 8.53 (d, J = 2.0 Hz, 1 H).	44	Similar to Example 1
Example 148	242	1.78-2.00 (m, 2 H), 2.20-2.31 (m, 2 H), 2.44-2.52 (m, 2 H), 2.68-2.82 (m, 8 H), 3.80 (s, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 7.12-7.30 (m, 11 H), 7.43 (d, J = 7.9 Hz, 1 H), 7.64 (ddd, J = 7.9, 7.6, 1.7 Hz, 1 H), 8.53 (ddd, J = 5.0, 1.7, 1.0 Hz, 1 H).	57	Similar to Example 1
Example 149	243	1.7-1.83 (m, 2 H), 2.1-2.25 (m, 2 H), 2.43 (t, J = 7.4 Hz, 2 H), 2.4-2.74 (m, 8 H), 3.69 (s, 2 H), 3.75 (s, 3 H), 3.96 (t, J = 7.7 Hz, 1 H), 6.81 (d, J = 8.9 Hz, 2 H), 7.16 (d, J = 8.6 Hz, 2 H), 7.2-7.35 (m, 7 H), 8.51 (d, J = 5.9 Hz, 2 H).	32	Similar to Example 1
Example 150	245	1.70-1.85 (m, 2 H), 2.12-2.22 (m, 2 H), 2.37-2.45 (m, 2 H), 2.63-2.72 (m, 8 H), 3.63 (s, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 7.15-7.29 (m, 11 H), 7.87 (d, J = 4.6 Hz, 2 H).	8	Similar to Example 1
Example 151	258	1.80-1.88 (dt, J = 12.2, 5.9 Hz, 2 H), 2.40 (dd, J = 6.0, 5.2 Hz, 2 H), 2.57-2.74 (m, 10 H), 3.63 (s, 2 H), 7.15-7.20 (m, 2 H), 7.26-7.32 (m, 6 H), 7.45-7.48 (m, 4 H), 8.52 (dd, J = 4.3, 1.6 Hz, 2 H).	8	Similar to Example 1

General Alkylation Procedure for 1-(3-Hydroxy-3,3-diphenylpropyl)homopiperazine for Examples 152-162.

A solution of 1-(3-hydroxy-3,3-diphenylpropyl)homopiperazine (0.12 mmol) in 0.5 mL of acetonitrile was treated with alkylating reagent (0.10 mmol) and potassium carbonate (0.15 mmol) and the reaction mixture was heated to 50 °C for 5 h. Polystyrene-linked benzyl isocyanate resin (0.65 mmol/g, 0.05 mmol) and dichloromethane (0.5 mL) was added and the mixture was stirred at room temperature for 1 h. The mixture was filtered and washed with dichloromethane (0.5 mL). The filtrate and washing were combined, and the solvent was removed under reduced pressure to afford the *N,N*-dialkylated material.

Example 152: Compound No. 174 (65 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 493.0 (M^++H, $C_{29}H_{36}N_2O_3S$).

Example 153: Compound No. 175 (51 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 507.5 (M^++H, $C_{30}H_{38}N_2O_3S$).

Example 154: Compound No. 176 (48 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 507.5 (M^++H, $C_{30}H_{38}N_2O_3S$).

Example 155: Compound No. 177 (51 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 521.5 (M^++H, $C_{31}H_{40}N_2O_3S$).

Example 156: Compound No. 178 (56 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 541.5 (M^++H, $C_{32}H_{36}N_2O_3S$).

Example 157: Compound No. 179 (41 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 479.0 (M^++1, $C_{28}H_{34}N_2O_3S$).

Example 158: Compound No. 180 (42 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 493.0 (M^++1, $C_{29}H_{36}N_2O_3S$).

Example 159: Compound No. 181 (42 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 507.5 (M^++1, $C_{30}H_{38}N_2O_3S$).

Example 160: Compound No. 182 (53 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 507.5 (M^++1, $C_{30}H_{38}N_2O_3S$).

Example 161: Compound No. 183 (40 mg) was prepared by above g neral alkylation procedure. ESI/MS *m/e* 521.5 (M^++1, $C_{31}H_{40}N_2O_3S$).

Example 162: Compound No. 184 (52 mg) was prepared by above general alkylation procedure. ESI/MS *m/e* 541.5 (M^++1, $C_{33}H_{36}N_2O_3S$).

Preparation of 1-(3,3-Diphenylpropyl)homopiperazine .

A suspension of homopiperazine (2.9 g, 28.9 mmol) and homopiperazine dihydrochloride (5.0 g, 28.9 mmol) in EtOH was heated to 70 °C for 2 h, at which point a homogeneous solution of monohydrochloride salt (2.5 equiv) was obtained. The reaction mixture was treated with 3,3-diphenylpropyl methanesulfonate (6.7 g, 23.1 mmol, 1 equiv) and NaI (8.65 g, 57.7 mmol, 2.5 equiv) and heated to reflux for 16 h. The reaction mixture was cooled to 25 °C and the solvent was removed in vacuo. The crude product was partitioned between 2N aqueous NaOH (100 mL) and EtOAc (100 mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with saturated aqueous NaCl (1 x 100 mL), dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 4 x 20 cm, 10% CH_3OH-5% Et_3N-CH_2Cl_2) afforded the monoalkylated product (6.44 g, 6.79 g theoretical, 95%) as an amber oil.

General Alkylation of 1-(3,3-Diphenylpropyl)homopiperazine for Examples 163-194.

A solution of 1-(3,3-diphenylpropyl)homopiperazine (132 mg, 0.449 mmol) was treated with alkylating reagent (0.492 mmol, 1.1 equiv) and Et_3N (75 mL, 0.54 mmol, 1.2 equiv) and the reaction mixture was heated to 70 °C for 16 h. The solvent was removed under vacuum. Chromatography (SiO_2, 2 x 20 cm, 20% CH_3OH-EtOAc) afforded the *N,N*-dialkylated material (10-95%).

Chromatography Methods.

HPLC analyses was performed with following methods.

1. Methods A and B.

Column

Method A: Micra Analytical Column (4.6 mm x 3.3 cm)

Method B: Monitor C18 column (50 mm x 4.6 mm)

Buffer for methods A and B

Buffer A: 0.05% TFA in H_2O

Buffer B: 0.035% TFA in 10% H_2O/CH_3CN

Gradient 1 (10-11 min)

1% Buffer B for 0.5 min

1 to 31% Buffer B in 5.0 min

31% to 51% Buffer B in 2.0 min

51% Buffer B for 0.5 min

51% to 1% Buffer B in 0.5 min

1% Buffer B Hold

Gradient 2 (4 min)

10% Buffer B for 0.5 min

61% Buffer B in 1.8 min

91% Buffer B in 1.5 min

91% Buffer B for 0.8 min

91% to 10% Buffer B in 0.4 min

10% Buffer B Hold

2. Method C

Column

C18 column 4.6 mm

Gradient

1% Buffer B for 3 min

1% to 61% Buffer B in 20 min

61% Buffer B For 4 min

61% to 1% Buffer B in 1 min

1% Buffer B for 5 min - hold

Example 163: Compound No. 265 (82 mg, 39%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (151.7 mg, 0.513 mmol) and *N,N*-diethylacetamide (78 mL, 0.567 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 4.93 min (90%), 220 nm (Method A); ESI/MS *m/e* 408.4 (M^++H, $C_{26}H_{37}N_3O$).

Example 164: Compound No. 210 (53 mg, 34%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (131 mg, 0.446 mmol) and 1-bromo-2-butyne (42 mL, 0.479 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 18.18 min (>90%), 220 nm (Method C); ESI/MS *m/e* 347.2 (M^++H, $C_{24}H_{30}N_2$).

Example 165: Compound N . 211 (102 mg, 75%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (115 mg, 0.391 mmol) and (bromomethyl)cyclopropane (42 mL, 0.433 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 17.91 min (>95%), 220 nm (Method C); ESI/MS *m/e* 349.4 (M^++H, $C_{24}H_{32}N_2$).

Example 166: Compound No. 266 (150 mg, 95%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (132 mg, 0.449 mmol) and 2-bromoacetamide (68 mg, 0.492 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 6.10 min (90%), 220 nm (Method A); ESI/MS *m/e* 352.2 (M^++H, $C_{22}H_{29}N_3O$).

Example 167: Compound No. 212 (21 mg, 9%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (151 mg, 0.513 mmol) and 7-acetoxy-4-(bromomethyl)coumarin (168 mg, 0.565 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 5.73 min (>90%), 220 nm (Method A); ESI/MS *m/e* 469.4 (M^++H, $C_{30}H_{32}N_2O_3$).

Example 168: Compound No. 213 (164 mg, 94%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (136.6 mg, 0.465 mmol) and 5-bromovaleronitrile (60 mL, 0.511 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 17.75 min (>90%), 220 nm (Method C); ESI/MS *m/e* 376.4 (M^++H, $C_{26}H_{33}N_3$).

Example 169: Compound No. 70 (132 mg, 89%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and 2-chloro-*N*-(2,6-diethylphenyl)acetamide (70 mg, 0.310 mmol, 0.9 equiv) employing general alkylation procedure. RPLC t_R = 6.97 min (88%), 220 nm (Method A); ESI/MS *m/e* 484.4 (M^++H, $C_{32}H_{41}N_3O$).

Example 170: Compound No. 214 (49 mg, 42%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and 3-bromopropionitrile (31 mL, 0.374 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 4.36 min (>90%), 220 nm (Method A); ESI/MS *m/e* 348.2 (M^++H, $C_{23}H_{29}N_3$).

Example 171: Compound No. 215 (71 mg, 58%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mm l) and 4-

bromobutyronitrile (37 mL, 0.374 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 3.91 min (86%), 220 nm (Method A); ESI/MS *m/e* 362.2 (M^++H, $C_{24}H_{31}N_3$).

Example 172: Compound No. 267 (31 mg, 24%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and *N*-ethylchloroacetamide (45 mg, 0.374 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 4.07 min (91%), 220 nm (Method A); ESI/MS *m/e* 380.4 (M^++H, $C_{24}H_{33}N_3O$).

Example 173: Compound No. 204 (29 mg, 17%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (105.4 mg, 0.359 mmol) and methyl 2-[3-(2-chloroethyl) ureido]benzoate (110 mg, 0.394 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 4.95 min (>95%), 220 nm (Method A); ESI/MS *m/e* 483.4 (M^++H, $C_{30}H_{35}N_4O_2$).

Example 174: Compound No. 216 (79 mg, 36%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (136.7 mg, 0.465 mmol) and Maybridge SPB03660 (108.8 mg, 0.511 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 5.83 min (>90%), 220 nm (Method A); ESI/MS *m/e* 471.4 (M^++H, $C_{29}H_{34}N_4O_2$).

Example 175: Compound No. 246 (59 mg, 33%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge GK02253 (87 mg, 0.374 mmol) employing general alkylation procedure. RPLC t_R = 5.11 min (>95%), 220 nm (Method A); ESI/MS *m/e* 491.4 (M^++H, $C_{28}H_{34}N_4O_2S$).

Example 176: Compound No. 217 (66 mg, 58%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and bromoacetonitrile (26 mL, 0.374 mmol) employing general alkylation procedure. RPLC t_R = 5.21 min (>95%), 220 nm; ESI/MS *m/e* 334.4 (M^++H, $C_{22}H_{27}N_3$).

Example 177: Compound No. 71 (59 mg, 33%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge CD08063 (100 mg, 0.374 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 6.23 min (>85%), 220 nm (Method A); ESI/MS *m/e* 525.2 (M^++H, $C_{28}H_{33}ClN_4O_2S$).

Example 178: Compound No. 247 (35 mg, 22%) was prepar d from 1-

(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge SEW03081 (63 mg, 0.374 mmol) employing general alkylation procedure. RPLC t_R = 6.20 min (90%), 220 nm (Method A); ESI/MS *m/e* 427.4 (M^++H, $C_{22}H_{27}ClN_4S$).

Example 179: Compound No. 74 (42 mg, 23%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge S52956 (85 mg, 0.374 mmol) employing general alkylation procedure. RPLC t_R = 21 min (90%), 220 nm (Method A); ESI/MS *m/e* 486.4 (M^++H, $C_{31}H_{39}N_3O_2$).

Example 180: Compound No. 248 (105 mg, 41%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (133.5 mg, 0.454 mmol) and Maybridge GK1350 (149 mg, 0.500 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 6.60 min (>90%), 220 nm (Method A); ESI/MS *m/e* 556.4 (M^++H, $C_{32}H_{37}N_5O_2S$).

Example 181: Compound No. 249 (80 mg, 34%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (126.7 mg, 0.430 mmol) and Maybridge RF00404 (134 mg, 0.474 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 5.96 min (>90%), 220 nm (Method A); ESI/MS *m/e* 540.4 (M^++H, $C_{28}H_{31}Cl_2N_5O_2$).

Example 182: Compound No. 219 (69 mg, 38%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge S07335 (117 mg, 0.408 mmol, 1.2 equiv) employing general alkylation procedure. RPLC t_R = 4.68 min (>95%), 220 nm (Method A); ESI/MS *m/e* 526.4 hydrolysis product (M^++H, $C_{36}H_{37}N_3O_2$).

Example 183: Compound No. 269 (20 mg, 13%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge CD07922 (67 mg, 0.374 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 4.65 min (90%), 220 nm (Method A); ESI/MS *m/e* 438.3 (M^++H, $C_{26}H_{36}N_3OS$).

Example 184: Compound No. 250 (24 mg, 19%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge SEW00285 (89 mg) employing general alkylation procedure. RPLC t_R = 4.70 min (>90%), 220 nm (Method A); ESI/MS *m/e* 377.3 (M^++H, $C_{23}H_{28}N_4O$).

Example 185: Compound No. 220 (67 mg, 63%) was prepared from 1-(3,3-diphenylpropyl)hom piperazine (100 mg, 0.340 mmol) and propargyl bromide

(38 mg, 0.32 mmol) and potassium iodide (0.037 g, 0.22 mmol) employing general alkylation procedure. TLC R_f = 0.29 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 4.21 min (>85%), 220 nm (Method A); ESI/MS *m/e* 333.3 (M^++H, $C_{23}H_{36}N_2$).

Example 186: Compound No. 221 (51 mg, 32%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(3-chloropropyl)-1,3-dihydro-2 *H*-benzimidazol-2-one (85 mg, 0.408 mmol) employing general alkylation procedure. RPLC t_R = 4.70 min (>97%), 220 nm (Method B); ESI/MS *m/e* 469.3 (M^++H, $C_{30}H_{36}N_4O$).

Example 187: Compound No. 222 was synthesized from 1-(3,3-diphenylpropyl)homopiperazine (200 mg, 0.680 mmol) and 2-(*tert*-butyldiphenylsilyl)-3-bromo-2-methyl-1-propanol (125 mg, 0.32 mmol) employing general alkylation procedure. R_f 0.53 (10% CH_3OH-CH_2Cl_2). The purified intermediate was dissolved in anhydrous THF and treated with *tert*-butylammonium fluoride (0.35 mL, 0.35 mmol, 1.1 equiv). The reaction mixture was stirred at 25 °C for 2 h and concentrated. Chromatography (SiO_2, 40 g, 20% CH_3OH-EtOAc) afforded the desired product (30 mg, 30%, two steps). TLC R_f 0.17 (conditions); RPLC t_R = 4.16 min (>85%), 220 nm (Method B); ESI/MS *m/e* 367.3 (M^++H, $C_{24}H_{34}N_2O$).

Example 188: Compound No. 75 (91 mg, 65%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and α-bromo-*o*-tolunitrile (80 mg, 0.406 mmol) employing general alkylation procedure. RPLC t_R = 6.52 min (>98%), 220 nm (Method B); ESI/MS *m/e* 410.3 (M^++H, $C_{28}H_{31}N_3$).

Example 189: Compound No. 76 (63 mg, 37%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and 2-bromoacetamido-4-nitrophenol (111 mg, 0.406 mmol) employing general alkylation procedure. RPLC t_R = 6.55 min (>98%), 220 nm (Method B); ESI/MS *m/e* 489.3 (M^++H, $C_{28}H_{32}N_4O_4$).

Example 190: Compound No. 77 (103 mg, 61%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and ethyl 4-(2-chloroacetamido) benzoate (98 mg, 0.406 mmol) employing general alkylation procedure. RPLC t_R = 6.52 min (>98%), 220 nm (Method B); ESI/MS *m/e* 500.3 (M^++H, $C_{31}H_{37}N_4O_3$).

Example 191: Compound No. 223 (84 mg, 49%) was prepared from 1-

(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and 1-(3-chloropropyl) theobromine (104 mg, 0.406 mmol) employing general alkylation procedure. RPLC t_R = 5.25 min (>98%), 220 nm (Method B); ESI/MS *m/e* 515.3 (M^++H, $C_{30}H_{38}N_6O_2$).

Example 192: Compound No. 80 (81 mg, 47%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and 4-nitrobenzyl bromoacetate (111 mg, 0.406 mmol) employing general alkylation procedure. RPLC t_R = 7.35 min (>98%), 220 nm (Method B); ESI/MS *m/e* 488.3 (M^++H, $C_{29}H_{33}N_3O_4$).

Example 193: Compound No. 81 (139 mg, 92%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and 2-hydroxy-5-nitrobenzyl bromide (90 mg, 0.406 mmol) employing general alkylation procedure. RPLC t_R = 5.90 min (>95%), 220 nm (Method B); ESI/MS *m/e* 446.3 (M^++H, $C_{27}H_{31}N_3O_3$).

Example 194: Compound No. 268 (34 mg, 25%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and *N*-(chloroacetyl)isopropylamine (51 mg, 0.374 mmol) employing general alkylation procedure. RPLC t_R = 5.47 min (>90%), 220 nm (Method B); ESI/MS *m/e* 394.4 (M^++H, $C_{25}H_{33}N_3O$).

General Epoxide Opening with 1-(3,3-Diphenylpropyl)homopiperazine for Examples 195-197.

A solution of 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) in CH_3CN (1.8 mL) was treated with epoxide (0.374 mmol, 1.1 equiv) and $^iPr_2NEt$ (71 mL, 0.41 mmol, 1.2 equiv), and the reaction mixture was heated to 70 °C for 16 h. The solvent was removed under reduced pressure. Chromatography (SiO_2, 2 x 20 cm, 20% CH_3OH-EtOAc) afforded the *N,N*-dialkylated material (23-83%).

Example 195: Compound No. 218 (114 mg, 83%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.340 mmol) and Maybridge NRB00767 (42 mg, 0.375 mmol) employing general epoxide opening procedure. RPLC t_R = 3.77 min (>85%), 220 nm (Method A); ESI/MS *m/e* 407.4 (M^++H, $C_{27}H_{36}N_2O_2$).

Example 196: Compound No. 253 (35 mg, 23%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.339 mmol) and furfuryl glycidyl ether (63 mg, 0.406 mmol) employing g neral epoxide opening pr cedure. RPLC

t_R = 5.70 min (>98%), 220 nm (Method B); ESI/MS *m/e* 449.3 (M^++H, $C_{28}H_{36}N_4O_3$).

Example 197: Compound No. 225 (69 mg, 70%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (40.3 mg, 0.137 mmol) and *N*-(2,3-epoxypropyl)phthalimide (42.6 mg, 0.150 mmol) employing general epoxide opening procedure. TLC R_f = 0.40 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.96 min (>85%), 220 nm (Method B-10 min); ESI/MS *m/e* 498.3 (M^++H, $C_{31}H_{35}N_3O_3$).

Preparation of *N,N*-Diethyl-(1-homopiperazinyl) acetamide.

Acetyl chloride (3.90 mL, 54.9 mmol) was dissolved in EtOH (166 mL) and the mixture was stirred for 30 min at 25 °C. A solution of homopiperazine (5.0 g, 50 mmol, 1 equiv) in EtOH (20 mL) was added to the reaction mixture in one portion. The flask was fitted with a reflux condenser with a $CaCl_2$ drying tube and the reaction mixture was heated to reflux for 1 h. *N,N*-Diethylchloroacetamide (3.37 g, 0.5 equiv) was added and the reaction was heated to reflux for an additional 16 h. The reaction mixture was allowed to cool and the solvent was removed in vacuo. The product was partitioned between EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with EtOAc (1 x 100 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated to yield the symmetrically dialkylated material (0.950 g, 17%). The aqueous phase was basicified with 1 M NaOH (100 mL) and was extracted CH_2Cl_2 (1 x 150 mL, 2 x 100 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated to afford the pure monoalkylated homopiperazine (2.4 g, 45%).

Preparation of 1-(4-Cyanobenzyl)homopiperazine.

To a solution of homopiperazine (9.2 g, 92 mmol, 2 equiv), in EtOH (115 mL) was added 1 M HCl-EtOH (92 mL) dropwise over 1 h. The suspension was heated to 70 °C for 1 h at which point a homogeneous solution of monohydrochloride salt was obtained. α-Bromo-*p*-tolunitrile (9.0 g, 46 mmol, 1 equiv) was added and the reaction mixture was heated to reflux for 5 h. After cooling, the solvent was removed by rotary evaporation and the residue was partitioned between CH_2Cl_2 (100 mL) and 2N aqueous KOH (100 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL) and the combined organic phase was washed with saturated aqueous NaCl (1 x 150 mL) and dried ($MgSO_4$). Chromatography (SiO_2, 4 x 20 cm, 20% CH_3OH - 5% Et_3N-CH_2Cl_2) afforded the desired monoalkylated material (6.78 g, 10.1 g theoretical, 67%) as an amber oil.

Preparation of 1-[4-(Methylsulfonyl)benzyl]homopiperazine.

To a 2-n ck, 2-L round bottom flask containing anhydrous EtOH (800 mL) and equipped with a mechanical stirr r and condenser was add d acetyl chlorid (20.2 mL, 0.267 mol, 1.1 equiv). The solution was stirred for 0.5 h and homopiperazine (24.3 g, 0.243 mol) was added. The mixture was heated to reflux for 2 h. The reaction mixture was cooled to 25 °C, 4-(methylsulfonyl)benzyl chloride (25 g, 0.122 mol, 0.5 equiv) was added and the reaction mixture heated to reflux for 16 h. The reaction mixture was cooled to 25 °C and the solvent was removed under vacuum. The residue was diluted with EtOAc (500 mL) and was washed with 2N KOH (2 x 500 mL). The aqueous layer was extracted with EtOAc (1 x 500 mL). The organic phase was combined, washed with 2N KOH (1 x 300 mL), dried ($MgSO_4$) and concentrated. The crude solid was washed with hot EtOAc to yield pure desired product (8.03 g, 32.7 g theoretical, 25%) as an off-white solid. TLC R_f 0.04 (10% CH_3OH-CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (br s, 1 H), 7.92 (d, J = 8.0 Hz, 2 H), 7.60 (d, J = 7.7 Hz, 2 H), 3.80 (br s, 2 H), 3.36 (br m, 2 H), 3.07 (s, 3 H), 2.93 (br s, 2 H), 2.80 (br s, 2 H), 2.12 (br m, 2 H)

Preparation of 1-(4-Picolyl)homopiperazine.

A solution of acetyl chloride (6.34 mL, 0.084 mol, 4 equiv) dissolved in anhydrous EtOH (50 mL) was stirred for 0.5 h and added to a solution of homopiperazine (10.4 g, 0.1 mol, 5 equiv) in EtOH (250 mL). The reaction mixture was heated to reflux for 1 h, cooled to 25 °C and a solution of 4-picolyl chloride hydrochloride 93.44 g, 0.021 mol) in EtOH (40 mL) was added. The reaction mixture was heated to reflux for 16 h, cooled to 25 °C and the solvent was removed under vacuum. The residue was diluted with CH_2Cl_2 (300 mL) and was washed with 2N KOH (1 x 300 mL). The aqueous layer was extracted with CH_2Cl_2 (1 x 300 mL) and the organic phase was washed with 2N KOH (150 mL), dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 5% H_2O-5% NH_4OH-^{i}PrOH) afforded the desired product (2.88 g, 4.01 g theoretical, 72%) as a yellow oil. TLC R_f 0.45 (5% H_2O-5% NH_4OH-^{i}PrOH): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.77 (d, J = 5.9 Hz, 2 H), 7.53 (d, J = 5.7 Hz, 2 H), 3.91 (s, 2 H), 3.19 (m, 4 H), 2.92 (m, 4 H), 2.04 (m, 2 H).

Preparation of 1-(4-Chlorobenzyl)homopiperazine.

Acetyl chloride (11.7 mL, 0.165 mol) was added to anhydrous EtOH (500 mL) and the mixture was stirred for 30 min at 25 °C. Homopiperazine (15.0 g, 0.150 mol) was added and the mixture was heated to reflux for 4 h. 4-Chlorobenzyl

chloride (13.96 g, 0.087 mol) was added and the reaction mixture was heated to r flux for 16 h before concentrating. The residue was dissolved in EtOAc (500 mL) and washed with 1N aqueous KOH (50 mL). The aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (double separation, SiO_2, 20 x 7 cm, ^iPrOH-H_2O-NH_4OH, 80:12:6 to 70:20:10 gradient elution) afforded the desired product (10.6 g, 53.4%) and the dialkylated homopiperazine (2.36 g, 16.5%). GC/MS *m/e* 224 (M^+, $C_{12}H_{17}N_2Cl$).10 % CH_3OH-CH_2Cl_2); RPLC t_R = 5.96 min (>85%), 220 nm (Mm (Method B); ESI/MS *m/e* 498.3 (M^++H, $C_{31}H_{35}N_3O_3$).

Preparation of 1-(4-Methyl-2-thienyl)-2-(1-homopiperazinylacetyl)hydrazine.

1-(*tert*-butyloxycarbonyl)homopiperazine (1.0 g, 5.0 mmol) in CH_3CN (25 mL) was treated with Maybridge GK 02253 (1.2 g, 5.0 mmol) and $^iPr_2NEt$ (1.04 mL, 6.0 mmol, 1.2 equiv). The reaction mixture was heated to 70 _C for 16 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by chromatography (SiO_2, 4 x 20 cm, 5% CH_3OH-CH_2Cl_2) to afford the Boc-protected monoalkylated material as a white foam (1.33 g, 67%). RPLC t_R = 5.20 min (>98%), 220 nm (Method B); ESI/MS *m/e* 397.0 (M^++H, $C_{18}H_{33}N_4O_4S$). The product (1.1 g, 2.8 mmol) was dissolved in 3 M HCl-CH_3OH (14 mL) and stirred at 25 _C for 30 min. The solvent was removed by rotary evaporation and the deprotected homopiperazine HCl salt was dissolved in ^tBuOH-H_2O (3:1, 25 mL). Dowex Anion exchange resin was added until pH = 9. The resin was removed by filtration and evaporation afforded the pure mono-alkylated product (703 mg, 86%). RPLC t_R = 0.78 min (>98%), 220 nm (Method B); ESI/MS *m/e* 297.1 (M^++H, $C_{14}H_{30}N_4O_2S$).

General Alkylation with 4-Bromo-2,2-diphenylbutyronitrile for Examples 198-203.

Monosubstituted homopiperazine (100 mg, 0.468 mmol, 1.0 equiv) in CH_3CN (3 mL) was treated sequentially with 4-bromo-2,2-diphenylbutyronitrile (168 mg, 0.561 mmol, 1.2 equiv) followed by $^iPr_2NEt$ (60 mg, 0.468 mmol, 1.2 equiv). The reaction mixture was heated to 70 °C with stirring for 16 h. The mixture was allowed to cool and the solvent was removed in vacuo. The product was purified by chromatography (SiO_2, 3 x 5 cm, 20% CH_3OH-EtOAc) to afford the desired dialkylated material (48 mg, 24%).

Example 198: Compound No. 264 (48 mg, 24%) was prepared from *N,N*-diethyl-(1-homopiperazinyl) acetamide (100 mg, 0.468 mmol) and 4-bromo-2,2-diphenylbutyronitrile (168 mg, 0.561 mmol) employing general alkylation procedure. TLC R_f = 0.30 (20% CH_3OH-EtOAc); RPLC t_R = 4.58 min (>98%), 220 nm (Method B); ESI/MS *m/e* 433.3 (M^++H, $C_{27}H_{36}N_4O$).

Example 199: Compound No. 233 (225 mg, 73%) was prepared from 1-(4-picolyl)homopiperazine (200 mg, 1.05 mmol) and 4-bromo-2,2-diphenylbutyronitrile (225 mg, 0.75 mmol) employing general alkylation procedure. TLC R_f = 0.33 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 4.27 min (>85%), 220 nm (Method B); ESI/MS *m/e* 411.3 (M^++H, $C_{27}H_{30}N_4$).

Example 200: Compound No. 2 (155 mg, 52%) was prepared from 1-(4-cyanobenzyl)homopiperazine (150 mg, 0.684 mmol) and 4-bromo-2,2-diphenylbutyronitrile (226 mg, 0.752 mmol, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 4.93 min (85.1%), 220 nm (Method B); ESI/MS *m/e* 435.3 (M^++H, $C_{29}H_{30}N_4$).

Example 201: Compound No. 3 (16 mg, 12%) was prepared from 1-(4-chlorobenzyl)homopiperazine (68 mg, 0.30 mmol) and 4-bromo-2,2-diphenylbutyronitrile (100 mg, 0.33 mmol) employing general alkylation procedure. TLC R_f = 0.32 (5% CH_3OH-CH_2Cl_2); RPLC t_R = 5.27 min (>85%), 220 nm (Method A); ESI/MS *m/e* 444.3 (M^++H, $C_{28}H_{30}ClN_2$).

Example 202: Compound No. 4 (251 mg, 69%) was prepared from 1-[4-(methylsulfonyl)benzyl]homopiperazine (200 mg, 0.75 mmol) and 4-bromo-2,2-diphenylbutyronitrile (270 mg, 0.9 mmol) employing general alkylation procedure. TLC R_f = 0.53 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 4.73 min (>85%), 220 nm (Method A); ESI/MS *m/e* 488.3 (M^++H, $C_{29}H_{33}N_2O_2S$).

Example 203: Compound No. 234 (9 mg, 5%) was prepared from 1-(4-methyl-2-thienyl)-2-(1-homopiperazinylacetyl)hydrazine (95 mg, 0.32 mmol) and 4-bromo-2,2-diphenylbutyronitrile (96 mg, 0.32 mmol) employing general alkylation procedure. RPLC t_R = 6.03 min (>90%), 220 nm (Method B-10 min); ESI/MS *m/e* 516.3 (M^++H, $C_{29}H_{33}N_5O_2S$).

Preparation of 1-(4-Cyanobenzyl)piperazine.

To a solution of piperazine (5.17 g, 60 mmol, 2 equiv) in EtOH (40 mL) was added 1 M HCl-EtOH (60 mL) dr pwise over 1 h and the suspension was heated to 70 °C for 1 h. α-Bromo-*p*-tolunitrile (5.88 g, 30 mmol, 1 equiv) was added and the reaction was heated to reflux for 16 h. After cooling the solvent was removed by rotary evaporation and the residue was partitioned between CH_2Cl_2 (70 mL) and 2N aqueous KOH (70 mL) and the combined organic phase was washed with saturated aqueous NaCl (100 mL) and dried ($MgSO_4$). Chromatography (SiO_2, 20% CH_3OH-5% Et_3N-CH_2Cl_2) afforded the monoalkylated material (2.6 g, 6.0 g theoretical, 43%) as an amber oil.

General Alkylation of 1-(4-Cyanobenzyl)piperazine for Examples 204 and 205.

A solution of 1-(4-cyanobenzyl)piperazine (150 mg, 0.745 mmol) was treated with alkylating reagent (0.745 mmol, 1 equiv) and $^iPr_2NEt$ (156 mL, 0.894 mmol, 1.2 equiv). The reaction mixture was heated to 70 °C and stirred by vortex for 16 h. After cooling, the reaction mixture was subjected directly to chromatography (SiO_2, 3-7% CH_3OH-CH_2Cl_2, gradient elution) to afford the desired *N,N*-dialkylated piperazine (11-77%).

Example 204: Compound No. 9 (142 mg, 48%) was prepared from 1-(4-cyanobenzyl)piperazine (150 mg, 0.745 mmol) and 3,3-diphenylpropyl methanesulfonate (216 mg, 0.745 mmol, 1 equiv) employing general alkylation procedure. RPLC t_R = 6.47 min (>95%), 220 nm (Method B); ESI/MS *m/e* 396.2 (M^++H, $C_{27}H_{29}N_3$).

Example 205: Compound No. 1 (166 mg, 53%) was prepared from 1-(4-cyanobenzyl)homopiperazine (150 mg, 0.745 mmol) and 4-bromo-2,2-diphenylbutyronitrile (224 mg, 0.745 mmol) employing general alkylation procedure. RPLC t_R = 6.82 min (>95%), 220 nm (Method B); ESI/MS *m/e* 422.3 (M^++H, $C_{28}H_{28}N_4$).

General Preparation of Hydrazide Alkylating Agents .

The hydrazide starting material (7.93 mmol) was dissolved in CH_3CN (20 mL) and treated with chloroacetyl chloride (0.95 mL, 11.93 mmol, 1.5 equiv) and Et_3N (1.11 mL, 7.96 mmol, 1.02 equiv). The mixture was stirred at 25 °C for 16 h and concentrated. The residue was dissolved in EtOAc (300 mL), washed with 1N aqueous HCl (10 mL) saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and

concentrated in vacuo. The desir d compound was isolated by trituration with EtOAc, foll wed by washing with hexane or chromatography (SiO_2). General alkylation procedure for Example 163-194 was then used to afford the desired homopiperazine analogs.

Example 206: 1-Benzoyl-2-(chloroacetyl)hydrazine (850 mg, 54%) was prepared from benzhydrazide (1.00 g, 7.34 mmol) and chloroacetyl chloride (0.58 mL, 7.34 mmol, 1 equiv) using general procedure. Compound No. 78 (300 mg, 51%) was prepared from 1-(3,3-diphenylpropyl) homopiperazine (100 mg, 0.34 mmol) and 1-benzoyl-2-(chloroacetyl)hydrazine (80 mg, 0.38 mmol) employing general alkylation procedure. TLC R_f = 0.44 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.85 min (>85%), 220 nm (Method B); ESI/MS *m/e* 471.3 (M^++H, $C_{29}H_{34}N_4O_2$).

Example 207: 1-(Chloroacetyl)-2-(phenylacetyl)hydrazine (1.24 g, 82%) was prepared from phenylacetohydrazide (1.00 g, 6.66 mmol) and chloroacetyl chloride (0.53 mL, 6.66 mmol, 1 equiv) using general procedure. Compound No. 79 (71 mg, 43%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(chloroacetyl)-2-(phenylacetyl)hydrazine (85 mg, 0.38 mmol) employing general alkylation procedure. TLC R_f = 0.40 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.02 min (>85%), 220 nm (Method B); ESI/MS *m/e* 485.5 (M^++H, $C_{30}H_{36}N_4O_2$).

Example 208: 1-(2-Furoyl)-2-(chloroacetyl)hydrazine (1.21 g, 75%) was prepared from 2-furoic acid hydrazide (1.06 g, 7.93 mmol) and chloroacetyl chloride (0.95 mL, 11.9 mmol, 1.5 equiv) using general procedure. Compound No. 251 (63 mg, 40%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(2-furoyl)-2-(chloroacetyl)hydrazine (76 mg, 0.38 mmol) employing general alkylation procedure. TLC R_f = 0.42 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.60 min (>85%), 220 nm (Method B); ESI/MS *m/e* 461.3 (M^++H, $C_{27}H_{32}N_4O_3$).

Example 209: 1-(2-Thiophenecarbo nyl)-2-(chloroacetyl)hydrazine (1.14 g, 74%) was prepared from 2-thiophenecarbo hydrazide (1.00 g, 7.03 mmol) and chloroacetyl chloride (0.86 mL, 10.6 mmol, 1.5 equiv) using general procedure. Compound No. 252 (88 mg, 54%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(2-Thiophenecarbonyl)-2-(chloroacetyl)hydrazine (82 mg, 0.38 mmol) employing general alkylation procedure. TLC R_f = 0.47 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.92 min (>85%), 220 nm (Method B); ESI/MS *m/e* 477.3 (M^++H, $C_{27}H_{32}N_4O_2S$).

Example 210: 1-(Diphenylcarbamoyl)-4-(2-chloroacetyl)semicarbazide (1.30 g, 65%) was prepared from 4,4-diphenylsemicarbazide (1.5 g, 6.60 mmol) and chloroacetyl chloride (0.79 mL, 9.92 mmol, 1.5 equiv) using general procedure. Compound No. 297 (46 mg, 24%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(diphenylcarbamoyl)-4-(2-chloroacetyl)semicarbazide (114 mg, 0.38 mmol) employing general alkylation procedure. TLC R_f =0.44 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.55 min (>85%), 220 nm (Method B); ESI/MS *m/e* 562.5 (M^++H, $C_{35}H_{39}N_5O_2$).

Example 211: 1-(Phenylcarbamoyl)-4-(2-chloroacetyl)semicarbazide (1.19 g, 67%) was prepared from 4-phenylsemicarbazide (1.00 g, 6.62 mmol) and chloroacetyl chloride (0.79 mL, 9.92 mmol) using general procedure. Compound No. 82 (33 mg, 20%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(phenylcarbamoyl)-4-(2-chloroacetyl)semicarbazide (85 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f = 0.41 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.96 min (>85%), 220 nm (Method B); ESI/MS *m/e* 486.4 (M^++H, $C_{29}H_{35}N_5O_2$).

Example 212: 1-(Ethylcarbamoyl)-2-(chloroacetyl)hydrazine (1.31 g, 76%) was prepared from ethyl carbazate (1.00 g, 9.61 mmol) and chloroacetyl chloride (1.15 mL, 10.16 mmol, 1 equiv) using general procedure. Compound No. 224 (81 mg, 54%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(ethylcarbamoyl)-2-(chloroacetyl)hydrazine (68 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f =0.44 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.91 min (>85%), 220 nm (Method B); ESI/MS *m/e* 439.3 (M^++H, $C_{34}H_{36}N_4O_3$).

Example 213: 1-(4-Nitrobenzoyl)-2-(chloroacetyl)hydrazine was prepared from 4-nitrobenzhydrazide (1.00 g, 5.52 mmol) and chloroacetyl chloride (0.66 mL, 8.29 mmol) using general procedure. Trituration from EtOAc gave the hydrazine in quantitative yield, which was used without further purification. Compound No. 86 (56 mg, 32%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(4-nitrobenzoyl)-2-(chloroacetyl)hydrazine (96 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f =0.46 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.56 min (>85%), 220 nm (Method A); ESI/MS *m/e* 516.3 (M^++H, $C_{29}H_{33}N_5O_4$).

Example 214: 1-(Toluoyl)-2-(chloroacetyl)hydrazine was prepared from 4-toluic hydrazide (1.00 g, 6.66 mmol) and chloroacetyl chloride (0.80 mL, 9.99 mmol) using general procedure. Trituration from EtOAc gave the hydrazine in quantitative yield, which was used without further purification. Compound No. 87 (61 mg, 37%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(toluoyl)-2-(chloroacetyl)hydrazine (74 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f = 0.44 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.51 min (>85%), 220 nm (Method A); ESI/MS *m/e* 485.4 (M^++H, $C_{30}H_{36}N_4O_2$).

Example 215: 1-(4-Hydroxybenzoyl)-2-(chloroacetyl)hydrazine was prepared from 4-hydroxybenzhydrazide (1.00 g, 6.57 mmol) and chloroacetyl chloride (0.79 mL, 9.92 mmol) using general procedure. Trituration from EtOAc gave the hydrazine in quantitative yield, which was used without further purification. Compound No. 89 (71 mg, 43%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(4-hydroxy benzoyl)-2-(chloroacetyl)hydrazine (85 mg, 0.37 mmol) employing general alkylation procedure. RPLC t_R = 6.21 min (>85%), 220 nm (Method B-10 min); ESI/MS *m/e* 487.3 (M^++H, $C_{29}H_{34}N_4O_3$).

Example 216: 1-(2-Nitrobenzoyl)-2-(chloroacetyl)hydrazine (0.579 g, 41%) was prepared from 2-nitrobenzhydrazide (1.00 g, 5.52 mmol) and chloroacetyl chloride (0.66 mL, 8.83 mmol) using general procedure. Compound No. 90 (82 mg, 47%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(2-nitro benzoyl)-2-(chloroacetyl)hydrazine (96 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f =0.40 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.04 min (>85%), 220 nm (Method B); ESI/MS *m/e* 516.1 (M^++H, $C_{29}H_{33}N_5O_4$).

Example 217: 1-(4-Methoxybenzoyl)-2-(chloroacetyl)hydrazine (1.783 g, 54%) was prepared from 4-methoxybenzhydrazide (1.00 g, 6.00 mmol) and chloroacetyl chloride (0.72 mL, 9.00 mmol) using general procedure. Compound No. 92 (63 mg, 51%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(4-methoxy benzoyl)-2-(chloroacetyl)hydrazine (91 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f = 0.52 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.46 min (>85%), 220 nm (Method A); ESI/MS *m/e* 501.1 (M^++H, $C_{30}H_{36}N_4O_3$).

Example 218: 1-(Nicotinoyl)-2-(chloroacetyl)hydrazine (1.29 g, 83%) was prepared from nicotinohydrazide (1.00 g, 7.29 mmol) and chloroacetyl chloride

(0.87 mL, 10.94 mmol) using g neral procedure. Compound No. 254 (100 mg, 66%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(nicotinoyl)-2-(chloroacetyl)hydrazine (87 mg, 0.41 mmol) employing general alkylation procedure. TLC R_f =0.12 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.61 min (93%), 220 nm (Method B); ESI/MS *m/e* 472.3 (M^++H, $C_{28}H_{33}N_5O_2$).

Example 219: 1-(2-Benzo[b]thiophenecarbonyl)-2-(chloroacetyl)hydrazine (0.578 g, 94%) was prepared from (2-benzo[b]thiophenecarbonyl)hydrazine (0.50 g, 2.60 mmol) and chloroacetyl chloride (0.31 mL, 3.90 mmol) using general procedure. Compound No. 255 (73 mg, 41%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(2-benzo[b]thiophenecarbonyl)-2-(chloroacetyl)hydrazine (88 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f =0.26 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.96 min (>85%), 220 nm (Method B); ESI/MS *m/e* 527.3 (M^++H, $C_{31}H_{34}N_4O_2S$).

Example 220: 1-(4-Bromobenzoyl)-2-(chloroacetyl)hydrazine (0.886 g, 73%) was prepared from 4-bromobenzhydrazide (1.00 g, 4.64 mmol) and chloroacetyl chloride (0.55 mL, 6.90 mmol) using general procedure. Compound No. 98 (143 mg, 76%) was prepared from 1-(3,3-diphenylpropyl)homopiperazine (100 mg, 0.34 mmol) and 1-(4-bromobenzoyl)-2-(chloroacetyl)hydrazine (98 mg, 0.37 mmol) employing general alkylation procedure. TLC R_f =0.50 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.76 min (>85%), 220 nm (Method B); ESI/MS *m/e* 551.0 (M^++H, $C_{29}H_{33}N_4O_2Br$).

Preparation of Sodium [4-(3,3-Diphenylpropyl)homopiperazine-1-yl]acetate.

1-(3,3-Diphenylpropyl)homopiperazine (2.0 g, 6.79 mmol) was dissolved in CH_3CN (60 mL) and treated with methyl bromoacetate (1.56 g, 10.18 mmol) and Et_3N (1.42 mL, 10.18 mmol). The mixture was refluxed for 18 h and subsequently concentrated in vacuo. The residue was subjected to flash silica gel column chromatography (eluent: CH_2Cl_2/MeOH, 96/4, v/v) to give Methyl [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (1.93 g) in 78% yield. TLC R_f = 0.53 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 4.71 min (>85%), 220 nm (Method A); ESI/MS *m/e* 367.1 (M^++H, $C_{23}H_{30}N_2O_2$).

Methyl [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (0.327 g, 0.89 mmol) was dissolved in a mixture of dioxane (3.1 mL), MeOH (1.1 mL) and 4N NaOH (0.22 mL). After stirring for 30 min, 5 more drops of 4N NaOH were added

and stirring was continued until hydrolysis of the methyl ester was complete. The mixture was concentrated in vacuo and the residue subjected to flash silica gel column chromatography (eluent: CH_2Cl_2/MeOH, 1/1, v/v) to give sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (0.278 g) in 88% yield. TLC R_f = 0.22 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 1.98 min (>85%), 220 nm (Method B); ESI/MS *m/e* 353.3 (M^++H, $C_{22}H_{29}N_2O_2$).

General Procedure for Coupling to Sodium [4-(3,3-Diphenylpropyl)homopiperazine-1-yl]acetate for Examples 221-253.

sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) was suspended in dry CH_2Cl_2 (1 mL) and HOBt (12 mg, 0.089 mmol) and the amine, hydrazide or amino acid (0.88 mmol) were added. After cooling the mixture to 0 _C, EDCI (30 mg, 0.10 mmol) was added, the pH adjusted to 7-8 with Et_3N and the mixture was stirred for 15 min at 0 _C and 16 h at rt. Concentration in vacuo of the mixture gave a residue which was not worked up but purified directly by HPLC.

Example 221: Compound No. 270 (55.6 mg, 70%) was prepared from sodium sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (53.6 mg, 0.15 mmol) and dihexylamine (39 mL, 0.167 mmol) employing general coupling procedure. TLC R_f =0.46 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 8.27 min (>85%), 220 nm (Method B); ESI/MS *m/e* 520.6 (M^++H, $C_{34}H_{53}N_3O$).

Example 222: Compound No. 83 (30 mg, 39%) was prepared sodium sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (60.2 mg, 0.17 mmol) and benzylhydrazine dihydrochloride (40 mg, 0.205 mmol) employing general coupling procedure. TLC R_f =0.39 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.16 min (>85%), 220 nm (Method B); ESI/MS *m/e* 457.3 (M^++H, $C_{29}H_{36}N_4O$).

Example 223: Methyl 2-benzoylhydrazinoacetate (0.418 g, 27%) was prepared from benzhydrazide (1.00g, 7.34 mmol) and methyl bromoacetate (0.76 mL, 80.3 mmol) employing general procedure. Compound No. 84 (37 mg, 44%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (56 mg, 0.158 mmol) and methyl 2-benzoylhydrazinoacetate (36 mg, 0.17 mmol) employing general coupling procedure. TLC R_f =0.49 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.21 min (>85%), 220 nm (Method B); ESI/MS *m/e* 543.1 (M^++H, $C_{32}H_{38}N_4O_4$).

Example 224: Compound No. 85 (59 mg, 75%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (62 mg, 0.166 mmol) and 2-aminoacetophenone hydrochloride (33 mg, 0.195 mmol) employing general coupling procedure. TLC R_f =0.40 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.51 min (>85%), 220 nm (Method A); ESI/MS *m/e* 470.3 (M^++H, $C_{30}H_{35}N_3O_2$).

Example 225: Compound No. 88 (41 mg, 58%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (50 mg, 0.14 mmol) and 4-chlorobenzhydrazide (27 mg, 0.156 mmol) employing general coupling procedure. RPLC t_R = 5.71 min (>85%), 220 nm (Method A); ESI/MS *m/e* 505.2 (M^++H, $C_{29}H_{33}N_4O_2Cl$).

Example 226: Compound No. 91 (55 mg, 68%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (60 mg, 0.16 mmol) and 2-amino-4'-methoxyacetophenone hydrochloride (36 mg, 0.176 mmol) employing general coupling procedure. TLC R_f =0.55 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.50 min (>85%), 220 nm (Method B); ESI/MS *m/e* 500.2 (M^++H, $C_{31}H_{37}N_3O_3$).

Example 227: Compound No. 271 (51 mg, 73%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (60 mg, 0.16 mmol) and dipropylamine (24 mL, 0.176 mmol) employing general coupling procedure. TLC R_f =0.56 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.51 min (>85%), 220 nm (Method A); ESI/MS *m/e* 436.3 (M^++H, $C_{28}H_{41}N_3O$).

Example 228: Compound No. 186 (34 mg, 23%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (100 mg, 0.267 mmol) and benzenesulfonohydrazide (54 mg, 0.31 mmol) employing general coupling procedure. TLC R_f =0.47 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.31 min (87%), 220 nm (Method B); ESI/MS *m/e* 507.5 (M^++H, $C_{28}H_{34}N_4O_3S$).

Example 229: Compound No. 93 (79 mg, 81%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (75 mg, 0.20 mmol) and 4-aminobenzhydrazide (34 mg, 0.22 mmol) employing general coupling procedure. TLC R_f =0.26 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.61 min (>85%), 220 nm (Method B); ESI/MS *m/e* 486.3 (M^++H, $C_{29}H_{35}N_5O_2$).

Example 230: C mpound No. 94 (24.4 mg, 17%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (100 mg, 0.267 mmol) and

4-methoxybenzenesulfonohydrazide (59.4 mg, 0.29 mmol) employing general c upling procedure. TLC R_f =0.45 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.71 min (>85%), 220 nm (Method B); ESI/MS *m/e* 537.3 (M^++H, $C_{29}H_{36}N_4O_4S$).

Example 231: Compound No. 95 (27.9 mg, 20%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (100 mg, 0.267 mmol) and p-toluenesulfonohydrazide (55 mg, 0.295 mmol) employing general coupling procedure. TLC R_f =0.52 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.91 min (>85%), 220 nm (Method B); ESI/MS *m/e* 521.3 (M^++H, $C_{29}H_{36}N_4O_3S$).

Example 232: Compound No. 272 (34 mg, 65%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and glycine methyl ester hydrochloride (10.6 mg, 0.084 mmol) employing general coupling procedure. TLC R_f =0.42 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.96 min (>85%), 220 nm (Method B); ESI/MS *m/e* 424.3 (M^++H, $C_{25}H_{33}N_3O_3$).

Example 233: Compound No. 273 (37 mg, 72%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and glycinamide hydrochloride (9.3 mg, 0.084 mmol) employing general coupling procedure. TLC R_f =0.32 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.76 min (>85%), 220 nm (Method B); ESI/MS *m/e* 409.3 (M^++H, $C_{24}H_{32}N_4O_2$).

Example 234: Compound No. 274 (24 mg, 47%) was prepared sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and glycine tert-butyl ester hydrochloride (14.1 mg, 0.084 mmol) employing general coupling procedure. This compound was purified by diluting with CH_2Cl_2, washing with $NaHCO_3$, brine, drying ($MgSO_4$), filtering and evaporating off the solvent in vacuo. Final purification by silica gel column chromatography. TLC R_f = 0.41 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.56 min (>85%), 220 nm (Method B); ESI/MS *m/e* 466.5 (M^++H, $C_{28}H_{39}N_3O_3$).

Example 235: Compound No. 275 (26.9 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and (D)-(-)-2-phenylglycinol (13.2 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.42 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.21 min (>85%), 220 nm (Method B); ESI/MS *m/e* 472.0 (M^++H, $C_{30}H_{37}N_3O_2$).

Example 236: Compound No. 226 (27.0 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)hom piperazine-1-yl]acetate (30 mg, 0.08 mmol) and (1*S*,2*R*)-(-)-cis-1-amino-2-indanol (14.3 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.42 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.36 min (>85%), 220 nm (Method B); ESI/MS *m/e* 484.0 (M^++H, $C_{31}H_{37}N_3O_2$).

Example 237: Compound No. 276 (24.9 mg, 20%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and (1*R*, 2*S*)-(+)-cis-1-amino-2-indanol (14.3 mg, 0.096 mmol) employing general coupling procedure. TLC R_f = 0.42 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.26 min (>85%), 220 nm (Method B); ESI/MS *m/e* 484.0 (M^++H, $C_{31}H_{37}N_3O_2$).

Example 238: Compound No. 277 (29.9 mg, 43%) was prepared sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and *dl*-octopamine hydrochloride (18.2 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.24 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.76 min (95%), 220 nm (Method B); ESI/MS *m/e* 488.0 (M^++H, $C_{30}H_{37}N_3O_2$).

Example 239: Compound No. 278 (28.3 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and *dl*-norphenylephrine hydrochloride (18.2 mg, 0.38 mmol) employing general coupling procedure. TLC R_f =0.24 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.91 min (>85%), 220 nm (Method B); ESI/MS *m/e* 488.0 (M^++H, $C_{30}H_{37}N_3O_3$).

Example 240: Compound No. 279 (27.7 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol (17.4 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.46 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.36 min (>85%), 220 nm (Method B); ESI/MS *m/e* 516.0 (M^++H, $C_{32}H_{41}N_3O_3$).

Example 241: Compound No. 280 (29.9 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and norephedrine hydrochloride (18.0 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.46 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.06 min (>85%), 220 nm (Method B); ESI/MS *m/e* 486.3 (M^++H, $C_{31}H_{39}N_3O_2$).

Example 242: Compound No. 281 (22.4 mg, 20%) was prepared from sodium

[4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and 2-amino-1-phenylethanol (16.2 mg, 0.118 mmol) employing general coupling procedure. TLC R_f = 0.53 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.11 min (>85%), 220 nm (Method B); ESI/MS *m/e* 472.3 (M^++H, $C_{30}H_{37}N_3O_2$).

Example 243: Compound No. **298** (26.9 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and 2-amino-1,3-propanediol (11.0 mg, 0.121 mmol) employing general coupling procedure. TLC R_f =0.16 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.51 min (>85%), 220 nm (Method B); ESI/MS *m/e* 426.0 (M^++H, $C_{25}H_{35}N_3O_3$).

Example 244: Compound No. **282** (26.9 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and L-phenylalaninol (17.8 mg, 0.118 mmol) employing general coupling procedure. TLC R_f =0.53 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.31 min (>85%), 220 nm (Method B); ESI/MS *m/e* 486.3 (M^++H, $C_{31}H_{39}N_3O_2$).

Example 245: Compound No. **283** (27.0 mg, 46%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-phenylalaninamide hydrochloride (19.3 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.25 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 2.16 min (>85%), 220 nm (Method B); ESI/MS *m/e* 499.4 (M^++H, $C_{31}H_{38}N_4O_2$).

Example 246: Compound No. **284** (24 mg, 42%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-aspartic acid dimethyl ester hydrochloride (19.0 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.46 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 2.16 min (>85%), 220 nm (Method B -); ESI/MS *m/e* 496.4 (M^++H, $C_{28}H_{37}N_3O_5$).

Example 247: Compound No. **285** (32.4 mg, 49%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-phenylalanine benzyl ester *p*-toluenesulfonic acid salt (34.3 mg, 0.08 mmol) employing general coupling procedure. TLC R_f =0.53 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 2.53 min (>85%), 220 nm (Method B); ESI/MS *m/e* 590.6 (M^++H, $C_{38}H_{43}N_3O_3$).

Example 248: Compound No. **286** (22.5 mg, 40%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and

DL-leucine methyl ester hydrochloride (17.5 mg, 0.096 mmol) employing general coupling procedure. TLC R_f =0.53 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 2.21 min (>85%), 220 nm (Method B); ESI/MS *m/e* 480.5 (M^++H, $C_{29}H_{41}N_3O_3$).

Example 249: Compound No. 287 (23 mg, 20%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-tyrosine methyl ester hydrochloride (22.3.0 mg, 0.096 mmol) employing general coupling procedure. RPLC t_R = 2.01 min (>85%), 220 nm (Method B); ESI/MS *m/e* 530.2 (M^++H, $C_{32}H_{39}N_3O_4$).

Example 250: Compound No. 288 (23.8 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-methionine methyl ester hydrochloride (19.2 mg, 0.096 mmol) employing general coupling procedure. RPLC t_R = 2.01 min (>85%), 220 nm (Method B); ESI/MS *m/e* 498.2 (M^++H, $C_{28}H_{39}N_3O_3S$).

Example 251: Compound No. 289 (21.6 mg, 30%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-Tryptophan methyl ester hydrochloride (24.5 mg, 0.096 mmol) employing general coupling procedure. RPLC t_R = 2.27 min (>85%), 220 nm (Method B); ESI/MS *m/e* 553.4 (M^++H, $C_{34}H_{40}N_4O_3$).

Example 252: Compound No. 299 (20.9 mg, 43%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (20.5 mg, 0.096 mmol) employing general coupling procedure. RPLC t_R = 2.12 min (>85%), 220 nm (Method B); ESI/MS *m/e* 548.4 (M^++H, $C_{36}H_{41}N_3O_2$).

Example 253: Compound No. 291 (23.8 mg, 41%) was prepared from sodium [4-(3,3-diphenylpropyl)homopiperazine-1-yl]acetate (30 mg, 0.08 mmol) and DL-methionine methyl ester hydrochloride (19.2 mg, 0.096 mmol) employing general coupling procedure. RPLC t_R = 2.21 min (>85%), 220 nm (Method B); ESI/MS *m/e* 484.4 (M^++H, $C_{27}H_{37}N_3O_3S$).

Preparation of [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide.

Methyl [4-(3,3-diphenylpropyl)-1-homopiperazinyl]acetate (0.607 g,

1.66 mmol) was dissolved in ethanol (20 mL) and hydrazine hydrate (1 mL) was added. The mixture was refluxed for 19 h and subsequently concentrated in vacuo. The residue was taken up in EtOAc, washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford the title compound as an oil (0.547 g) in 90% yield. TLC R_f = 0.35 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 1.93 min (>85%), 220 nm (Method B); ESI/MS *m/e* 367.1 (M^++H, $C_{22}H_{30}N_4O$).

General Coupling Procedure for [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide for Examples 254-256.

[4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide (60.5 mg, 0.165 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and CH_3CN (0.5 mL). Pyridine (19 mL, 0.23 mmol) and the sulfonyl chloride (0.195 mmol) were added and the mixture was stirred at room temperature for 16 h. After concentration of the mixture in vacuo, flash silica gel column chromatography was used to isolate the desired product.

Example 254: Compound No. 96 (69 mg, 70%) was prepared from [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide (65 mg, 0.177 mmol) and *N*-acetylsulfanilyl chloride (46 mg, 0.195 mmol) employing general coupling procedure. TLC R_f = 0.35 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.36 min (>85%), 220 nm (Method B); ESI/MS *m/e* 564.3 (M^++H, $C_{30}H_{37}N_5O_4S$).

Example 255: Compound No. 97 (63.5 mg, 71%) was prepared from [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide (60.5 mg, 0.165 mmol) and 4-chlorobenzenesulfonyl chloride (38.3 mg, 0.181 mmol) employing general coupling procedure. RPLC t_R = 7.01 min (>85%), 220 nm (Method B); ESI/MS *m/e* 541.3 (M^++H, $C_{28}H_{33}N_4O_3SCl$).

Example 256: Compound No. 256 (40 mg, 53%) was prepared from [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide (55 mg, 0.15 mmol) and 2-thiophenesulfonyl chloride (30 mg, 0.164 mmol) employing general coupling procedure. RPLC t_R = 6.61 min (>85%), 220 nm (Method B); ESI/MS *m/e* 513.3 (M^++H, $C_{26}H_{32}N_4O_3S_2$).

Example 257: Compound No. 99 (55 mg, 64%) was prepared by dissolving [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide (51 mg, 0.139 mmol) in dry CH_2Cl_2 (2 mL) and adding HOBt (21 mg, 0.155 mmol) and 4-

(methylsulfonyl)benz ic acid (29 mg, 0.146 mmol). This mixture was c oled (0 _C) and treated with EDCI (45 mg, 0.151 mmol) follow d by Et_3N such that the pH was around 8. After stirring for 16 h at room temperature, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was applied to silica gel column chromatography (eluent: gradient of 96/4 to 94/6 CH_2Cl_2/MeOH, v/v) to afford the desired compound. TLC R_f =0.45 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.06 min (>85%), 220 nm (Method B); ESI/MS *m/e* 549.3 (M^++H, $C_{30}H_{36}N_4O_4S$).

Example 258: Compound No. 100 (45 mg, 64%) was prepared by dissolving [4-(3,3-Diphenylpropyl)-1-homopiperazinyl]acetohydrazide (49 mg, 0.134 mmol) in dry CH_2Cl_2 (2 mL) and adding HOBt (20 mg, 0.148 mmol) and 4-acetylbenzoic acid (23 mg, 0.14 mmol). This mixture was cooled (0 _C) and treated with EDCI (44 mg, 0.148 mmol) followed by Et_3N such that the pH was around 8. After stirring for 16 h at room temperature, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was applied to silica gel column chromatography (eluent: gradient of 96/4 to 94/6 CH_2Cl_2/MeOH, v/v) to afford the desired compound. TLC R_f =0.46 (10% CH_3OH-CH_2Cl_2); RPLC t_R = 6.26 min (>85%), 220 nm (Method B); ESI/MS *m/e* 513.3 (M^++H, $C_{31}H_{36}N_4O_3$).

Example 259: Compound No. 290 (6.6 mg, 64%) was prepared by treatment of Compound No. 286 (10.5 mg, 0.015 mmol) with 0.44 mL of 0.25 N LiOH (MeOH/H_2O, 3/1, v/v) at room temperature for 16 h. After acidifying the reaction mixture with TFA and evaporating off the solvents, the residue was purified using a small C-18 column (eluent: water followed by MeOH). RPLC t_R = 2.28 min (>85%), 220 nm (Method B); ESI/MS *m/e* 466.4 (M^++H, $C_{28}H_{39}N_3O_3$).

Example 260: Compound No. 292 (6.0 mg, 64%) was prepared by treatment of Compound No. 289 (9.6 mg, 0.0123 mmol) with 0.35 mL of 0.25 N LiOH (MeOH/H_2O, 3/1, v/v) at room temperature for 16 h. After acidifying the reaction mixtu e with TFA and evaporating off the solvents, the residue was purified using a sm C-18 column (eluent: water followed by MeOH). RPLC t_R = 2.41 min (>85%), 2.) nm (Method B); ESI/MS *m/e* 539.3 (M^++H, $C_{33}H_{38}N_4O_3$).

Example 261: Preparation of Compound No. 69.

A soluti n of 1-[4-(methylsulfonyl)benzyl]homopiperazine (314 mg, 1.17

mmol) in CH_3CN (50 mL) was treated sequentially with 3-[4-(tert-butoxycarbonyl)phenyl]-3- phenylpr pyl methanesulfonate (456 mg, 1.17 mmol, 1 equiv) and Na_2CO_3 (124 mg, 1.17 mmol, 1 equiv). The reaction mixture was heated to 70 °C for 16 h, cooled to 25 °C, filtered and concentrated. Chromatography (SiO_2, 2 x 20 cm, 5% CH_3OH-CH_2Cl_2) afforded the desired material (346 mg, 53%) RPLC t_R = 7.63 min (>90%), 220 nm (Method A); ESI/MS *m/e* 563.2 (M^++H, $C_{33}H_{42}N_2O_4S$).

Example 262: Preparation of Compound No. 72 and 73.

A solution of compound No. 69 (278 mg, 0.494 mmol) in CH_3OH (2 mL) was treated with a 1.0 M solution of HCl-Et_2O (5 mL) and stirred at 25 °C for 1 h. Concentration and chromatography (SiO_2, 2 x 20 cm, 5% CH_3OH-CH_2Cl_2 to CH_3OH, gradient elution) afforded the compound No. 72 (132 mg, 51%) and compound No. 73 (88 mg, 35%). Compound No. 72: RPLC t_R = 4.78 min (>90%), 220 nm (Method A); ESI/MS *m/e* 521.2 (M^++H, $C_{30}H_{36}N_2O_4S$). For compound No. 73: RPLC t_R = 4.08 min (>95%), 220 nm (Method A); ESI/MS *m/e* 507.2 (M^++H, $C_{29}H_{34}N_2O_4S$).

Example 263: Preparation of 1-(*tert*-Butyloxycarbonyl)-4-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 294).

1. A solution of di-*tert*-butyl dicarbonate (25 g, 115 mmol.) in CH_2Cl_2 (100 mL) was added over a period of 20 min to a solution of homopiperazine (57 g, 5.0 equiv) in CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temperature for 3 days. H_2O (150 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an oil which was purified by simple distillation to give 1-(*tert*-butyloxycarbonyl)homopiperazine: 13.68 g, 59% yield, colorless oil; The purity was determined by GC/MS (95%), m/e 200.1 (M^+, $C_{10}H_{20}N_2O_2$).

2. 3-Chloropropiophenone (7.14 g, 24.4 mmol), K_2CO_3 (8.79 g, 1.50 equiv) and KI (1.41 mg, 0.2 equiv) were added to a solution of the purified 1-(*tert*-butyloxycarbonyl)homopiperazine (8.486 g, 42.4 mmol) in CH_3CN (60 mL). The reaction mixture was stirred at 70 °C for 17 h and then AcOEt (200 mL) was added to the cooled mixture. The precipitated solid was removed by filtration and washed with AcOEt (50 mL). The combined filtrate was evaporated to afford an oil which was purified by column chromatography (SiO_2, 0%-20% CH_3CN/AcOEt) to give 1-(*tert*-Butyloxycarbonyl)-4-(3-phenyl-3-oxopropyl)homopiperazine : 11.27 g, 80% yield, pale yellow il; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40-1.65 (m, 9 H),

1.80-1.95 (m, 2 H), 2.65-2.85 (m, 4 H), 3.01 (t, 2 H, J = 6.9 Hz), 3.19 (t, 2 H, J = 6.9 Hz),.3.35-3.55 (m, 4 H), 7.47 (t, 2 H, J = 7,7 Hz), 7.55-7.65 (m, 1 H), 7.90-8.02 (m, 2 H). The purity was determined by RPLC/MS (Method B). RPLC t_R = 5.53 min (95%), 220 nm; ESI/MS *m/e* 333.4 (M^++H, $C_{19}H_{29}N_2O_3$).

3. A solution of 3-(*tert*-butyldimethylsilyloxy)phenylmagnesium bromide [prepared from 3-(*tert*-butyldimethylsilyloxy)bromobenzene (28.5 g, 99.2 mmol) and magnesium turnings (2.30 g, 94.5 mmol) in Et_2O (65 mL)] was added at 0 _C to a solution of the purified 1-(*tert*-Butyloxycarbonyl)-4-(3-phenyl-3-oxopropyl)homopiperazine (11.25 g, 33.8 mmol) in dry THF (150 mL). The mixture was warmed to room temperature with stirring and the stirring was continued for 3 h. Saturated aqueous NH_4Cl (300 mL) was added to the reaction mixture, the mixture was stirred for 15 min and extracted with AcOEt (3 x 150 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an oil (31.00 g) which was purified by column chromatography (SiO_2, 3%-25% AcOEt/hexane) to give 1-(*tert*-butyloxycarbonyl)-4-[3-{3-(*tert*-butyldimethylsilyloxy)phenyl}-3-hydroxy-3-phenylpropyl]homopiperazine : 9.00 g, 49% yield, pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 6 H), 0.81 (s, 9 H), 1.32 (s, 9 H), 1.4-1.5 (m, 2 H), 1.7-1.8 (m, 2 H), 2.2-2.3 (m, 2 H), 2.4-2.55 (m, 4 H), 3.25-3.45 (m, 4 H), 6.50-6.56 (m, 1 H), 6.80-6.92 (m, 2 H), 6.99-7.10 (m, 2 H), 7.11-7.20 (m, 2 H), 7.28-7.34 (m, 2 H). The purity was determined by RPLC/MS (Method A). RPLC t_R = 7.13 min (>95%), 220 nm; ESI/MS *m/e* 541.3 (M^++H, $C_{31}H_{49}N_2O_2Si$).

4. A solution of tetrabutylammonium fluoride (1.0 M solution in THF, 4.0 mL, 4.0 mmol, 1.03 equiv) was added to a solution of the purified 1-(*tert*-butyloxycarbonyl)-4-[3-{3-(*tert*-butyldimethylsilyloxy)phenyl}-3-hydroxy-3-phenylpropyl]homopiperazine (2.11 g, 3.90 mmol) in THF (35 mL). The mixture was stirred at room temperature for 30 min. H_2O (100 mL) was added to the reaction mixture and the mixture was extracted with AcOEt (3 x 100 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an oil (3.11 g) which was purified by column chromatography (SiO_2, 50% AcOEt/hexane) to give 1-(*tert*-butyloxycarbonyl)-4-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (compound No. 294): 1.381 g, 83% yield, colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 3 H), 1.50 (s, 6 H), 1.9-2.1 (m, 2 H), 2.45-2.9 (m, 8 H), 3.3-3.8 (m, 4 H), 6.7-7.0 (m, 2 H), 7.05-7.28 (m, 2 H), 7.3-7.38 (m, 2 H), 7.42-7.50 (m, 2 H). The purity

was determined by RPLC/MS (Meth d A). RPLC t_R = 5.30 min (>95%), 220 nm; ESI/MS *m/e* 427.3 (M^++H, $C_{25}H_{35}N_2O_4$).

Example 264: Preparation of 1-[3-Hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295).

p-Toluenesulfonic acid monohydrate (1.90 g, 10.0 mmol, 4.0 equiv) was added to a solution of the purified 1-(*tert*-butyloxycarbonyl)-4-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 294, 1.066 g, 2.50 mmol) in CH_3CN (15 mL). The reaction mixture was stirred at room temperature for 2.0 h and then, H_2O (50 mL) and CH_3OH (20 mL) were added. Anion exchange resin (11.5 g, DOWEX 1x2-200, washed with aqueous NaOH) was added and the mixture was gently agitated at room temperature for 5 min. The resin was removed by filtration and washed with CH_3OH (300 mL). The combined filtrate was evaporated to afford an oil (1.35 g) which was purified by column chromatography (SiO_2, 5%->10% CH_3OH, 5% TEA/CH_2Cl_2) to give 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295): 657 mg, 81% yield, colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.8 - 2.0 (m, 2 H), 2.35-2.45 (m, 2 H), 2.55-2.80 (m, 6 H), 3.0-3.15 (m, 4 H), 6.68-6.75 (m, 1 H), 6.82-6.88 (m, 1 H), 7.10-7.38 (m, 5 H), 7.42-7.52 (m, 2 H). The purity was determined by RPLC/MS (Method B). RPLC t_R = 4.27 min (>99%), 220 nm; ESI/MS *m/e* 327.3 (M^++H, $C_{20}H_{27}N_2O_2$).

Example 265: General Alkylation of 1-[3-Hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Preparation of Compound No. 185).

1-Benzoyl-2-(chloroacetyl)hydrazine (60 mg, 0.281 mmol, 1.2 equiv) and Et_3N (118 mg, 1.17 mmol, 5.0 equiv) were added to a solution of 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 100 mg, 0.306 mmol) in CH_3CN (2.0 mL). The reaction mixture was stirred at 60-70 °C for 13 h. The solvent was evaporated to afford an oil which was purified by column chromatography (SiO_2, 10% CH_3OH/CH_2Cl_2) to give Compound No. 185: 71 mg, 46% yield, colorless oil; ^1H NMR (CD_3OD, 300 MHz) δ 1.85-2.00 (m, 2 H), 2.45-2.55 (m, 2 H), 2.65-2.75 (m, 2 H), 2.78-3.00 (m, 8 H), 3.36 (s, 2 H), 6.62-6.65 (m, 1 H), 6.90-6.98 (m, 2 H), 7.10-7.35 (m, 4 H), 7.40-7.65 (m, 5 H), 7.88 (d, 2 H, J = 5.4 Hz). The purity was determined by RPLC/MS (Method B). RPLC t_R = 5.08 min (>98%), 220 nm; ESI/MS *m/e* 503.2 (M^++H, $C_{29}H_{35}N_4O_4$).

Example 266: Compound No. 259, di-TFA salt (54.8 mg, 15%) was prepared

from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]hom piperazine (Compound No. 295, 158 mg, 0.486 mmol) and Maybridge GK02253 (136 mg, 1.2 equiv) employing general alkylation procedure. The product was purified by preparative RPLC. RPLC t_R = 4.60 min (>98%), 220 nm (Method A); ESI/MS *m/e* 523.2 (M^++H, $C_{28}H_{35}N_4O_4S$).

Example 267: Compound No. 227 (20 mg, 35%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 36 mg, 0.11 mmol) and *N*-(3-bromopropyl)phthalimide (32 mg, 1.1 equiv) employing general alkylation procedure. RPLC t_R = 5.23 min (98%), 220 nm (Method B); ESI/MS *m/e* 514.3 (M^++H, $C_{31}H_{36}N_3O_4$).

Example 268: Compound No. 227260 (105 mg, 67%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 100 mg, 0.306 mmol) and 1-(chloroacetyl)-2-(2-thiophenecarbonl)hydrazine (61 mg, 1.2 equiv) employing general alkylation procedure. RPLC t_R = 4.95 min (>98%), 220 nm (Method B); ESI/MS *m/e* 509.2 (M^++H, $C_{27}H_{33}N_4O_4S$).

Example 269: Compound No. 261 (94 mg, 53%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 100 mg, 0.306 mmol) and Maybridge RF00404 (79 mg, 1.2 equiv) employing general alkylation procedure. RPLC t_R = 5.52 min (>98%), 220 nm (Method B); ESI/MS *m/e* 572.2 (M^++H, $C_{28}H_{32}Cl_2N_5O_4$).

Example 270: Compound No. 293 (65 mg, 48%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 100 mg, 0.306 mmol) and *N,N*-diethylacetamide (150 mg, 4.3 equiv) employing general alkylation procedure. RPLC t_R = 4.68 min (89%), 220 nm (Method B); ESI/MS *m/e* 440.2 (M^++H, $C_{26}H_{38}N_3O_3$).

Example 271: Compound No. 228 (97 mg, 63%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 100 mg, 0.306 mmol) and 1-(3-chloropropyl)-1,3-dihydro-2 *H*-benzimidazol-2-one (230 mg, 4.6 equiv) employing general alkylation procedure. t_R = 4.98 min (>95%), 220 nm (Method B); ESI/MS *m/e* 501.1 (M^++H, $C_{36}H_{37}N_4O_3$).

Example 272: Compound No. 229 (60 mg, 63%) was prepared from 1-[3-

hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]h mopiperazine (Compound No. 295, 59 mg, 0.182 mmol) and 4-brom -2-butenyl phenyl sulfone (50 mg, 1.0 equiv) employing general alkylation procedure. RPLC t_R = 5.20 min (>95%), 220 nm (Method B); ESI/MS *m/e* 521.3 (M^++H, $C_{30}H_{37}N_2O_4S$).

Example 273: Compound No. 262 di-TFA salt (88 mg, 48%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 80 mg, 0.245 mmol) and 1-(chloroacetyl)-2-(5-methylthiophenecarbonl)hydrazine (68 mg, 1.2 equiv) employing general alkylation procedure. The Product was purified by preparative RPLC. RPLC t_R = 5.23 min (>98%), 220 nm (Method B); ESI/MS *m/e* 523.3 (M^++H, $C_{28}H_{35}N_4O_4S$).

Example 274: Compound No. 187 di-TFA salt (19 mg, 9.5%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 80 mg, 0.245 mmol) and Salor S2,688-4 (88 mg, 1.2 equiv) employing general alkylation procedure. The Product was purified by preparative RPLC. RPLC t_R = 5.22 min (>85%), 220 nm (Method B); ESI/MS *m/e* 589.0 (M^++H, $C_{33}H_{37}N_2O_6S$).

Example 275: Compound No. 189 (26 mg, 42%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 40 mg, 0.123 mmol) and *N*-(phenacyl)chloroacetamide (32 mg, 1.2 equiv) employing general alkylation procedure. RPLC t_R = 5.73 min (>98%), 220 nm (Method B); ESI/MS *m/e* 502.3 (M^++H, $C_{30}H_{36}N_3O_4$).

Preparation of 1-[4-(Bromomethyl)benzenesulfonyl]pyrrole.

NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) was added to a solution of pyrrole (67 mg, 1.0 mmol) in THF (2.0 mL) and the mixture was stirred at room temperature for 5 min. Then 4-(bromomethyl)benzenesulfonyl chloride (269 mg, 1.0 mmol) was added to the mixture. After stirring at room temperature for additional 10 min, brine (15 mL) was added and the mixture was extracted with AcOEt (40 mL x 2). The combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an oil which was purified by column chromatography (SiO_2, 10% AcOEt/hexane) to give 1-[4-(bromomethyl)benzenesulfonyl]pyrrole: 46 mg, 15% yield, colorless oil. The purity was determined by GC/MS (>95%), *m/e* 299 (M^+, $C_{11}H_{10}NO_2BrS$).

Example 276: Compound No. 190 (27 mg, 40%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 40 mg, 0.123 mmol) and 1-[4-(bromomethyl)benzenesulfonyl]pyrrole (46 mg, 1.24 equiv) employing general alkylation procedure. RPLC t_R = 5.85 min (>98%), 220 nm (Method B); ESI/MS *m/e* 546.3 (M^++H, $C_{31}H_{36}N_3O_4S$).

Example 277: Compound No. 191 (39 mg, 61%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 40 mg, 0.123 mmol) and 1-(chloroacetyl)-2-(4-hydroxybenzoyl)hydrazine (28 mg, 1.0 equiv) employing general alkylation procedure. RPLC t_R = 4.72 min (>95%), 220 nm (Method B); ESI/MS *m/e* 519.3 (M^++H, $C_{29}H_{35}N_4O_5$).

Example 278: Compound No. 194 di-TFA salt (39 mg, 42%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 40 mg, 0.123 mmol) and 1-(chloroacetyl)-2-(4-chlorobenzoyl)hydrazine (31 mg, 1.0 equiv) employing general alkylation procedure. The Product was purified by preparative RPLC. RPLC t_R = 5.48 min (>95%), 220 nm (Method B); ESI/MS *m/e* 537.0 (M^++H, $C_{29}H_{34}ClN_4O_5$).

Example 279: Compound No. 195 di-TFA salt (30 mg, 33%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 40 mg, 0.123 mmol) and 1-chloroacetyl-4-phenylsemicarbazide (28 mg, 1.0 equiv) employing general alkylation procedure. The Product was purified by preparative RPLC. RPLC t_R = 5.18 min (>95%), 220 nm (Method B); ESI/MS *m/e* 518.3 (M^++H, $C_{29}H_{36}N_5O_4$).

Example 280: Compound No. 231 di-TFA salt (29 mg, 42%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 30 mg, 0.092 mmol) and bromobimane (28 mg, 1.0 equiv) employing general alkylation procedure. The product was purified by preparative RPLC. RPLC t_R = 1.87 min (>95%), 220 nm (Method B); ESI/MS *m/e* 517.4 (M^++H, $C_{30}H_{37}N_4O_4$).

Example 281: Compound No. 196 di-TFA salt (33 mg, 46%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 30 mg, 0.092 mmol) and Maybridge CD08063 (29 mg, 1.2 equiv) employing general alkylation procedure. The product was purified by preparative RPLC. RPLC t_R = 2.07 min (>98%), 220 nm (Method B); ESI/MS *m/e* 557.2 (M^++H, $C_{28}H_{34}ClN_4O_4S$).

Example 282: Compound No. 232 tri-TFA salt (6.6 mg, 9.1%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 30 mg, 0.092 mmol) and Maybridge BTB12299 (18 mg, 1.2 equiv) employing general alkylation procedure. The product was purified by preparative RPLC. RPLC t_R = 1.48 min (>95%), 220 nm (Method B); ESI/MS *m/e* 451.2 (M^++H, $C_{25}H_{31}N_4O_4$).

Example 283: Compound No. 296 (16 mg, 18%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 78 mg, 0.24 mmol) and acetyl chloride (19 mg, 1.0 equiv). Acetyl chloride and Et_3N (121 mg, 1.2 mmol, 5.0 equiv) were added to a solution of 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295) in CH_3CN (2.0 mL). The reaction mixture was stirred at room temperature for 30 min. saturated aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture and the mixture was extracted with AcOEt (3 x 15 mL). The combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an oil which was purified by column chromatography (SiO_2, 3-10% CH_3OH/CH_2Cl_2) to give 1-acetyl-4-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 296): 16 mg, 18% yield, colorless oil; RPLC t_R = 4.75 min (89%), 220 nm (Method B); ESI/MS *m/e* 369.3 (M^++H, $C_{22}H_{29}N_2O_3$).

Example 284: Compound No. 263 TFA salt (40 mg, 23%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 80 mg, 0.25 mmol), 2-(4-chlorobutyryl)thiophene (70 mg, 0.3 mmol) and triethylamine (174 mL, 1.25 mmol) employing general alkylation procedure. TLC R_f = 0.58 (5% Et_3N-10% CH_3OH-CH_2Cl_2); RPLC t_R = 4.98 min (>85%), 220 nm (Method B); ESI/MS *m/e* 479.3 (M^++H, $C_{28}H_{34}N_2O_3S$).

Example 285: Compound No. 188 TFA salt (31 mg, 17%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 80 mg, 0.25 mmol), 3-chloropropyl *p*-tolyl sulfone (70 mg, 0.3 mmol) and triethylamine (174 mL, 1.25 mmol) employing general alkylation procedure. TLC R_f = 0.62 (5% Et_3N-10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.25 min (>85%), 220 nm (Method B); ESI/MS *m/e* 523.3 (M^++H, $C_{30}H_{38}N_2O_4S$).

Example 286: Compound No. 192 TFA salt (34 mg, 19%) was prepared from

1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 80 mg, 0.25 mmol), 4-(chloroacetyl)catechol (56 mg, 0.3 mmol) and triethylamine (174 mL, 1.25 mmol) employing general alkylation procedure. TLC R_f = 0.62 (5% Et_3N-10% CH_3OH-CH_2Cl_2), RPLC t_R = 4.68 min (>85%), 220 nm (Method B); ESI/MS *m/e* 477.3 (M^++H, $C_{28}H_{32}N_2O_5$).

Example 287: Compound No. 230 TFA salt (30 mg, 17%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 80 mg, 0.25 mmol), glycidyl methacrylate (43 mg, 0.3 mmol) and triethylamine (174 mL, 1.25 mmol) employing general alkylation procedure. TLC R_f = 0.6 (5% Et_3N-10% CH_3OH-CH_2Cl_2), RPLC t_R = 4.95 min (90%), 220 nm (Method B); ESI/MS *m/e* 469.0 (M^++H, $C_{27}H_{36}N_2O_5$).

Example 288: Compound No. 193 TFA salt (44 mg, 49%) was prepared from 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 50 mg, 0.15 mmol), 2-chloro-4'-fluoro-3'-nitroacetanilide (50 mg, 0.12 mmol) and triethylamine (104 mL, 0.75 mmol) employing general alkylation procedure. TLC R_f = 0.6 (5% Et_3N-10% CH_3OH-CH_2Cl_2); RPLC t_R = 5.78 min (>85%), 220 nm (Method B); ESI/MS *m/e* 523.0 (M^++H, $C_{28}H_{31}N_4O_5F$).

Preparation of 1-[3-(3-Hydroxyphenyl)-3-phenylpropyl]homopiperazine.

1. Trifluoroacetic acid (4.75 mL) was added to a solution of 1-[3-hydroxy-3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (Compound No. 295, 60 mg, 0.184 mmol) in CH_2Cl_2 (0.25 mL). The reaction mixture was stirred at room temperature for 2.5 h. The trifluoroacetic acid was evaporated to afford 1-[3-(3-hydroxyphenyl)-3-phenyl-2-propenyl]homopiperazine as a colorless oil used without further purification.

2. A solution of 1-[3-(3-hydroxyphenyl)-3-phenyl-2-propenyl]homopiperazine in EtOH (6 mL) was hydrogenated at 1 atm for 1.5 h in the presence of 5% palladium on charcoal (60 mg) at room temperature. The catalyst was removed by filtration through Celite and washed with EtOH (30 mL). The combined filtrate was evaporated to give 1-[3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine (2TFA salt, 100 mg, quantitative) as a white solid used without further purification.. RPLC t_R = 1.62 min (Method B); ESI/MS *m/e* 311.2 (M^++H, $C_{20}H_{27}N_2O$).

Example 289: General Alkylation of 1-[3-(3-Hydroxyphenyl)-3-phenylpropyl]homopiperazine (Preparation of Compound No. 257).

Maybridge GK02253 (17 mg, 0.074 mmol, 1.2 equiv) and Et_3N (37 mg, 0.37 mmol, 6.0 equiv) were added to a solution of 1-[3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine 2TFA salt (33 mg, 0.061 mmol) in CH_3CN (2.0 mL). The reaction mixture was stirred at 70 °C for 15 h. The solvent was evaporated to afford an oil which was purified by preparative RPLC to give Compound No. 257 di-TFA salt: 8.0 mg, 18% yield, colorless oil. The purity was determined by RPLC/MS. RPLC t_R = 1.90 min (>95%), 220 nm (Method B); ESI/MS *m/e* 507.2 (M^++H, $C_{28}H_{35}N_4O_3S$).

Example 290: Compound No. 101 di-TFA salt (6.0 mg, 14%) was prepared from 1-[3-(3-hydroxyphenyl)-3-phenylpropyl]homopiperazine di-TFA salt (33 mg, 0.061 mmol) and *N*-(phenacyl)chloroacetamide (16 mg, 1.2 equiv) employing general alkylation procedure. The product was purified by preparative RPLC. RPLC t_R = 1.92 min (>85%), 220 nm (Method B); ESI/MS *m/e* 486.2 (M^++H, $C_{30}H_{36}N_3O_3$).

Preparation of 1-(3,3-Diphenylpropyl)piperazine.

1-(*tert*-butyloxycarbonyl)piperazine (1.00 g, 5.4 mmol) was dissolved in CH_3CN (27 mL) and was treated with 3,3-diphenylpropyl mesylate (1.6 g, 5.6 mmol, 1.05 equiv) and ^{i}PrNEt (1.40 mL, 8.05 mmol, 1.5 equiv). The reaction mixture was heated to 70 _C for 16 h, cooled and concetrated. The residue was purified by chromatography (SiO_2, 1% CH_3OH-CH_2Cl_2) to afford the desired Boc-protected material (988 mg, 48%). The product was treated with 3 M HCl-CH_3OH (26 mL) and stirred at 25 _C for 1 h. The solvent was removed in vacuo and the residue was dissolved in ^{t}BuOH-H_2O (26 mL). Dowex 500 anion exchange resin was added until pH = 9. The resin was filtered and solution concetrated to afforded the desired product (702 mg, 98%).

General Alkylation of 1-(3,3-Diphenylpropyl)piperazine.

1-(3,3-Diphenylpropyl)piperazine (50 mg, 0.178 mmol) was dissolved in CH_3CN (1 mL) and was treated with alkylating agent (0.196 mmol, 1.1 equiv) and ^{i}PrNEt 40 µL, 0.232 mmol, 1.3 equiv). The reaction mixture was heated to 70 _C for 16 h. The solvent was removed and the samples were purified by normal column chromatography or preparative RPLC.

Example 291: Compound No. 236 (di-TFA salt, 72 mg, 53%) was prepared

from 1-(3,3-diphenylpropyl)piperazine (50 mg, 0.178 mmol) and Maybridge GK 02253 (46 mg, 0.196 mmol) employing general alkylation procedure. RPLC t_R = 2.12 min (>90%), 220 nm (Method A); ESI/MS *m/e* 477.2 (M^++H, $C_{27}H_{32}N_4O_2S$).

Example 292: Compound No. 10 (di-TFA salt, 36 mg, 27%) was prepared from 1-(3,3-diphenylpropyl)piperazine (50 mg, 0.178 mmol) and *N*-(phenacyl)chloroacetamide (42 mg, 0.196 mmol) employing general alkylation procedure. RPLC t_R = 2.41 min (>95%), 220 nm (Method A); ESI/MS *m/e* 456.5 (M^++H, $C_{29}H_{33}N_3O_2$).

Example 293: Compound No. 11 (di-TFA salt, 76 mg, 57%) was prepared from 1-(3,3-diphenylpropyl)piperazine (50 mg, 0.178 mmol) and 1-benzoyl-2-(chloroacetyl)hydrazine (42 mg, 0.196 mmol) employing general alkylation procedure. RPLC t_R = 2.26 min (>95%), 220 nm (Method A); ESI/MS *m/e* 457.4 (M^++H, $C_{28}H_{32}N_4O_2$).

Example 294: Compound No. 12 (di-TFA salt, 54 mg, 46%) was prepared from 1-(3,3-diphenylpropyl)piperazine (50 mg, 0.178 mmol) and 2-hydroxy-5-nitrobenzyl bromide (46 mg, 0.196 mmol) employing general alkylation procedure. RPLC t_R = 2.20 min (>95%), 220 nm (Method A); ESI/MS *m/e* 432.2 (M^++H, $C_{26}H_{29}N_3O_3$).

Example 295: Compound No. 13 (43 mg, 49%) was prepared from 1-(3,3-diphenylpropyl)piperazine (50 mg, 0.178 mmol) and *N*-(4-methoxy-2-nitrophenyl)-2-bromoacetamide (46 mg, 0.196 mmol) employing general alkylation procedure. RPLC t_R = 2.66 min (>95%), 220 nm (Method A); ESI/MS *m/e* 489.2 (M^++H, $C_{28}H_{32}N_4O_4$).

Example 296: Compound No. 14 (55 mg, 62%) was prepared from 1-(3,3-diphenylpropyl)piperazine (50 mg, 0.178 mmol) and *N*-(4-acetamido-3-methoxyphenyl)-2-bromoacetamide (46 mg, 0.196 mmol) employing general alkylation procedure. RPLC t_R = 2.27 min (>95%), 220 nm (Method A); ESI/MS *m/e* 501.2 (M^++H, $C_{30}H_{36}N_4O_3$).

Example 297: Measurement of Inhibition of MIP-1α Binding to THP-1 Cells by Test Compounds.

Human monocytic leukemia cell line THP-1 was suspended in assay buffer (RPMI-1640 (Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH

7.4) to give a cell suspension of a concentration of 1 x 10^7 cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. Iodinated human MIP-1α (DuPont NEN Co.) was diluted in assay buffer to 250 nCi/mL and used as the ligand solution. In a 96 well filter plate (Millipore Co.), 25 μL of test compound solution, 25 μL of labeled ligand solution and 50 μL of cell suspension were aliquoted into each well in this order, stirred (total reaction volume 100 μL), and incubated for one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 200 μL of cold PBS (200 μL of cold PBS was added and then filtered). The filter was removed and placed in an RIA tube (Iuchi Seieido Co.) and the radioactivity retained by the cells on the filter were measured using a gamma counter (Aloka Co.).

To calculate the ability of test compounds to inhibit binding of human MIP-1α to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MIP-1α (Peprotech Co.) in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

Inhibition (%) = {1 - (A - B)/(C - B)} x 100

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MIP-1α added; C, counts with [^{125}I]-labeled human MIP-1 α added).

When inhibition by the cyclic diamine derivative of this invention was measured, for example, the following compounds demonstrated >20% inhibitory activity at 100 μM. These compounds are compound Nos. 1, 2, 3, 9, 34, 50, 52, 53, 54, 57, 59, 63, 64, 65, 66, 71, 75, 76, 78, 79, 80, 81, 82, 106, 107, 108, 109, 111, 112, 123, 197, 204, 210, 211, 212, 213, 215, 216, 218, 220, 221, 222, 223, 233, 246, 250, 252, 253, 258, 264, 265, 269, 270, and 297.

Example 298: Measurement of Inhibition of MCP-1 Binding to THP-1 Cells.

1. Construction of recombinant baculovirus carrying the human MCP-1 gene

Based on the previously published human MCP-1 gene sequence (for example T. Yoshimura et al., Febs Letters, 1989, 244, 487-493), two synthetic DNA primers

(5'-CACTCTAGACTCCAGCATGA-3' and 5'-TAGCTGCAGATTCTTGGGTTG-3') flanked by restriction enzyme sites wer used to amplify a DNA fragment fr m cDNA derived from human endothelial cells (purchased from Kurabow Co.); the amplified fragment was cut with the restriction enzymes (PstI and XbaI), ligated into a transfer vector pVL1393 (Invitrogen Co.), and the resulting vector was co-transfected along with infectious baculovirus into Sf-9 insect cells and the supernatant was plaque assayed to yield human MCP-1 gene baculovirus recombinant.

2. Synthesis of [^{125}I]-labeled human MCP-1 expressed in baculovirus

Using the method of K. Ishii et al. (Biochem Biophys Research Communications 1995, 206, 955-961), 5 x 10^6 Sf-6 insect cells was infected with 5 x 10^7 PFU (plaque forming units) of the above human MCP-1 recombinant baculovirus and cultured for 7 days in Ex-Cell 401 medium. The culture supernatant was affinity purified using a heparin Sepharose column (Pharmacia Co.) and then further purified using reverse phase HPLC (Vydac C18 column) to prepare purified human MCP-1. The purified human MCP-1 was protein labeled by Amersham Co. using the Bolton Hunter method to yield [^{125}I]-labeled baculovirus expressed human MCP-1 (specific activity 2000 Ci/ mmol).

3. Measurement of inhibition of binding of [^{125}I]-labeled baculovirus expressed human MCP-1 to THP-1 cells

Human monocytic leukemia cell line THP-1 was suspended in assay buffer (RPMI-1640 (Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 1 x 10^7 cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. [^{125}I]-labeled human MCP-1 described above was diluted in assay buffer to 1 mCi/mL and used as the labeled ligand solution. In a 96 well filter plate (Millipore Co.), 25 µL of test compound solution, 25 µL of labeled ligand solution and 50 µL of cell suspension were aliquoted into ach well in this order, stirred (total reaction volume 100 µL), and incubated or one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 200 µL of cold PBS (200 µL of cold PBS was added and then filtered). The filter was removed and placed in an RIA tube (Iuchi Seieido Co..), and the radioactivity retained by the cells on the filter wer measured using

a gamma counter (Aloka Co.).

To calculate the ability of test compound to inhibit binding of human MCP-1 to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MCP-1 in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

Inhibition (%) = (1 - (A - B)/(C - B)) x 100

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MIP-1α added; C, counts with [^{125}I]-labeled human MCP-1 added).

When inhibition by the cyclic diamine derivative of this invention was measured, for example, the following compounds demonstrated >20% inhibitory activity at 100 μM. These compounds are compound Nos. 1, 2, 3, 4, 9, 10, 11, 36, 50, 51, 52, 55, 56, 58, 59, 61, 63, 64, 65, 67, 68, 69, 72, 73, 75, 76, 78, 80, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 96, 98, 99, 100, 101, 103, 104, 106, 107, 108, 109, 114, 116, 117, 119, 121, 122, 123, 124, 125, 126, 128, 129, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 145, 146, 147, 148, 149, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 213, 214, 215, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 236, 246, 248, 249, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 267, 269, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 284, 287, 288, 293, 294, 295, 296, 298, and 299.

Example 299: Measurement of Inhibition of Binding of [^{125}I]-Labeled Human MCP-1 to Cells Expressing the MCP-1 Receptor.

1. Derivation of cells expressing the MCP-1 receptor

cDNA fragment containing the MCP-1 receptor reported by S. Yamagami et al., Biochemical Biophysical Research Communications 1994, 202, 1156-1162) was cloned into the expression plasmid pCEP4 (Invitrogen Co.) at the NotI site, and the plasmid obtained was transfected into the human kidney epithelial cell line 293-EBNA using the Lipofectamine reagent (Gibco-BRL Co.). The cells were

cultur d in the presence of the selective agent (Hygromycin), and a stably expressing transfectant line was obtained. The expression of the receptor was confirmed by binding of [^{125}I]-labeled human MCP-1.

2. Measurement of inhibition of binding of [^{125}I]-labeled baculovirus expressed human MCP-1 to the MCP-1 receptor expressing cells

The MCP-1 receptor expressing cells on tissue culture dishes were scraped using a cell scraper and suspended in assay buffer (D-MEM(Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 6 x 10^6 cells/mL. The test compound was diluted in the assay buffer to concentrations of 0.16, 0.8, 4, 20, and 100 μM. The remainder of the procedure was as described in Example 163.

When inhibition by the cyclic diamine derivative of this invention was measured, compound No. 36 for example showed dose dependent inhibition with 50% inhibitory concentration (IC_{50}) of 17 μM.

Example 300: Measurement of Inhibition of Cell Chemotaxis.

In order to determine the inhibition of cell chemotaxis by the compounds of this invention, we measured cell chemotaxis caused by monocyte chemotactic factor MCP-1 using the human monocytic leukemia cell line THP-1 as the chemotactic cell according to the method of Fall et al. (J. Immunol. Methods, 190, 33, 239-247). 2 x 10^6 cells/mL of THP-1 cells (suspended in RPMI-1640 (Flow Laboratories Co.) + 10% FCS) was placed in the upper chamber (200 μL) of a 96 well micro-chemotaxis chamber (Neuroprobe, registered tradename), and human recombinant MCP-1 in a same solution (Peprotech Co.) at a final concentration of 20 ng/mL was placed in the lower chamber, with a polycarbonate filter (PVP-free, Neuroprobe; registered tradename) placed between the two chambers. These were incubated at 37 °C for 2 hr in 5% CO_2.

The filter was removed, and the cells which had migrated to the underside of the filter was fixed, stained using Diff Quick (Kokusai Shiyaku Co.) and then quantitated using a plate reader (Molecular Device Co.) at a wavelength of 550 nm to determine the index of cell migration as a mean of 3 wells. In addition, test compounds were placed in the upper chamber along with THP-1, and the inhibition of cell migration (inhibition IC_{50} (μM)) was determined. Inhibition

was defined as {(cells migration induced MCP-1 with no test compound in the upper chamber) - (cells migration with no MCP-1 added in the lower chamber) = 100%}, and the concentration of the test compound which gave 50% inhibition was designated IC_{50}.

When the inhibition of cyclic diamine derivatives of the present invention was measured, the 50% inhibition concentration (IC_{50}) for compound No. 36 was 9 μM and for compound No. 240 was 30 μM.

Example 301: Inhibition of Delayed Type Hypersensitivity Reaction in the Mouse DNFB Induced Contact Hypersensitivity Model.

7 week old male Balb/c mice (Charles River Co.) were maintained for 1 week, after which the hair was shaved with an electric razor from the abdomen to the chest. 1 day and 2 days later, the shaved areas were painted twice with 25 μL of 0.5% dinitrofluorobenzene (DNFB) (Wako Pure Chemicals Co.) in acetone:olive oil = 4:1. At day 6, both side of the right ear was painted for an induction with 10 μL of 0.2% dinitrofluorobenzene (DNFB) (Wako Pure Chemicals Co.) in acetone:olive oil = 4:1, while the left ear was painted with 10 μL of acetone:olive oil = 4:1 not containing DNFB. As a test agent, compound No. 36 or compound No. 240 was dissolved in acetone to 20 mg/mL, and applied twice at 30 min before and after the DNFB induction (25 μL/ear/dose).

In the control group (no drug administration group), the acetone solution not containing any test compound was applied. There were 8 mice per group in both the control group and the experimental group. In order to prevent licking off of the DNFB and test compound, the necklace for mice were used during the study (Natsume Seisakujo Co.). At 48 hr after DNFB induction, ear lobes were sampled using a spring loaded micrometer (Ozaki Seisakujo Co.). The change in the ear lobe thickness was calculated according to the following formula.

Increase = 100 x ((right ear lobe thickness after sensitization - right ear lobe thickness prior to sensitization)/right ear lobe thickness prior to sensitization - (left ear lobe thickness after sensitization - left ear lobe thickness prior to sensitization)/left ear lobe thickness prior to sensitization)

After exanguination, the isolated ear was fixed in formalin, and

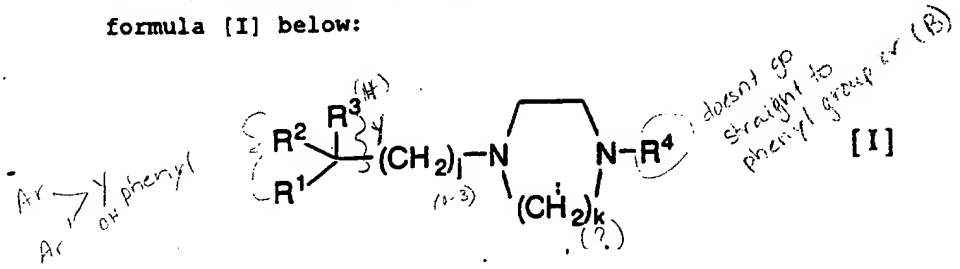
hematoxylin-eosin stained histopathological sections w re prepared for image analysis. Using a digital camera (Fuji Color Service, HC-1000) installed on an upright microscope and a personal computer (Macintosh 8100/100AV, using Photoshop software), the color images were digitized, and analyzed using a second image analysis software (NIH Image). The parameters measured were epidermal thickening, edema (area of dermal and subcutaneous tissues), and cellular infiltration of tissue (number of nuclei in the dermis and subcutaneous tissues).

Both compounds showed significant inhibitory activity.

Claims

What is claimed is:

1. A cyclic diamine selected from the group consisting of a compound of the formula [I] below:



[I]

and a pharmaceutically acceptable acid addition salt thereof

wherein R^1 and R^2 are the same or different from each other and are an unsubstituted or substituted phenyl group or aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, nitrogen atoms or combinations thereof, in which the phenyl or aromatic heterocyclic group may be substituted by one or more halogen atoms, hydroxy groups, C_1-C_8 lower alkyl groups, C_1-C_6 lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, C_1-C_6 hydroxyalkyl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoylamino groups, dioxolanyl groups, or by group represented by the formula: $-NR^5R^6$, or is condensed with a benzene ring to form a condensed ring, wherein the substituents for the phenyl or aromatic heterocyclic group and the condensed ring condensed with a benzene ring are one or more groups selected from halogen atoms, hydroxy groups, or C_1-C_6 lower alkoxy groups, and R^5 and R^6 are the same or different from each other and are hydrogen atoms, C_1-C_6 lower alkyl groups, or C_2-C_6 lower alkenyl groups;

R^3 represents a hydrogen atom, hydroxy group, cyano group, C_1-C_6 lower alkoxy group or C_2-C_7 lower alkanoyloxy group;

j represents an integer of 0-3;

k represents 2 or 3;

R^4 is a group represented by:

1) $-A^1-R^7$

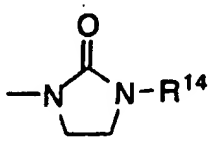
wherein R^7 is an unsubstituted or substituted phenyl group which may be substituted with one ore more groups which are the same or different and are halogen atoms, hydroxy groups, amino groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyl groups, C_1-C_6 alkylsulfonyl groups, trifluoromethylsulfonyl groups, unsubstituted phenylsulfonyl groups or

substituted with a hydroxy group, 1-pyrrolylsulfonyl groups, C_1-C_6 hydroxyalkylsulfonyl groups, C_1-C_6 alkanoylamino groups, or a group represented by the formula: $-CONR^8R^9$ in which R^8 and R^9, are the same or different from each other, and ar hydrogen atoms or C_1-C_6 lower alkyl groups; A^1 is a group represented by the formula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G represents G^1 or G^2, wherein G^1 represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$, and G^2 is $-(C=NH)NH-SO_2-$, $-CO-NH-NH-CO-$, $-CO-NH-NH-CO-NR^{10}-$, $-CO-NH-CH_2-CO-$, $-CO-NH-NH-SO_2-$, or $-CO-N(CH_2-CO-OCH_3)-NH-CO-$, R^{10} is a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; and q represents 0 or 1;

2) $-A^2-R^{11}$

wherein A^2 is -CO- or $-SO_2-$; R^{11} is:

a) and unsubstituted or substituted phenyl group wherein the substituents are one or more groups which are the same or different and are halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



b) an unsubstituted or substituted aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, nitrogen atoms or combinations thereof, wherein the substituents are one or more groups which are the same or different and are halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, or

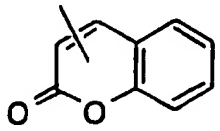
c) a group of the formula: $-CH_2-NR^{15}R^{16}$,

where R^{12}, R^{13}, R^{14} and R^{15} are the same or different groups, and are hydrogen atoms or C_1-C_6 lower alkyl groups and R^{16} is an unsubstituted or substituted phenyl group or a phenylalkyl group, wherein the substituents are one or more of the samenor different groups and are halogen atoms, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group;

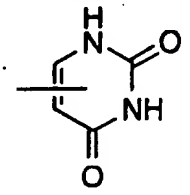
3) $-(CH_2)_n-R^{17}$

wherein R^{17} is a group which may be substituted at any possible sites by one ore more of the same or different groups and are halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, or C_1-C_6 lower alkoxy groups, repr s nting

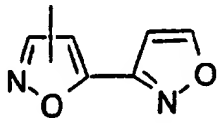
a hydrogen atom, cyano group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 hydroxyalkyl group, C_1-C_6 lower alkynyl group, C_3-C_6 cycloalkyl group, C_3-C_7 alkenoyl group, a group represented by the formula: $-(CHOH)CH_2OR^{18}$, a group r presented by the formula: $-CO-NH-NH-CO-OR^{19}$, a group represented by the formula:



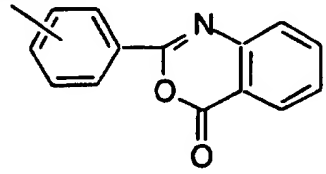
a group represented by the formula:



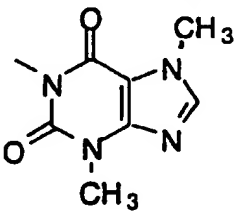
a group represented by the formula:



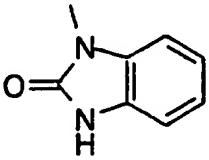
a group represented by the formula:



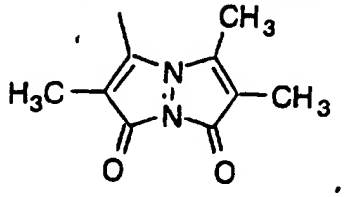
a group represented by the formula :



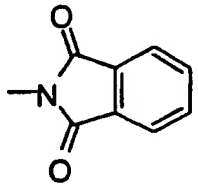
a group represented by the formula:



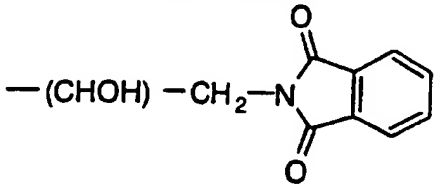
a group represented by the formula:



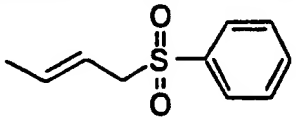
a group represented by the formula:



a group represented by the formula:

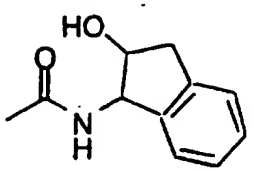


a group represented by the formula:



, or

a group represented by the formula:



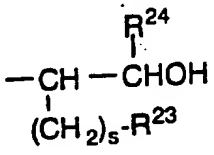
in which n is an integer of 1-4; R^{18} is a C_1-C_6 lower alkyl group, C_2-C_6 lower alkenyl group, or C_2-C_6 lower alkynyl group and R^{19} is a C_1-C_6 lower alkyl group;

4) $-(CH_2)_r-A^3-R^{20}$

wherein r represents an integer of 0-3; A^3 represents a single bond, -CO-, -CO-NH-NH-CO-, -CO-NH-NH-CO-NH-, -CO-NH-CH_2-CO-, -CO-NH-NH-SO_2-, -(CHOH)-CH_2-, or -(CHOH)-CH_2OCH_2-; R^{20} represents an aromatic heterocyclic group containing 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, nitrogen atoms or combinations thereof in which the aromatic heterocyclic group may be substituted by one or more groups which are the same or different and are halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, or pyrrolyl groups or is condensed with a benzene ring to form a condensed ring; or

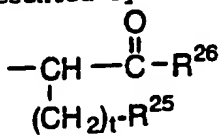
5) $-CH_2-CO-NR^{21}R^{22}$

wherein R^{21} is a hydrogen atom or a C_1-C_6 lower alkyl group; R^{22} represents a hydrogen atom, C_1-C_6 lower alkyl group, or a group represented by the formula:



;or

a group represented by the formula:



;

or R^{21} and R^{22}, taken together with the nitrogen to which they are attached form a 4 to 7-membered saturated heterocycle, which may contain an oxygen atom, sulfur atom, or another nitrogen atom; where s represents 0 or 1; t represents an integer of 0-2; R^{23} represents a hydrogen atom, hydroxy group, phenyl group, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group; R^{24} represents a hydrogen atom or phenyl group which may be substituted by hydroxy group; R^{25} represents a hydrogen atom, phenyl group which may be substituted by a hydroxy

group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 lower alkyl group, C_1-C_6 alkylthio group, or 3-indolyl group; and R^{26} represents a hydroxy group, amino group, C_1-C_6 lower alkoxy group, or ph nylalkyloxy group;

Wuth the proviso that when R^3 is a hydrogen atom, then j is not 0, R^7 is not hydroxy, C_1-C_6 lower alkyl or C_1-C_6 lower alkoxy; G^1 is not -O- or -CO-; its substituents, if R^{11} is a phenyl group, are not C_1-C_6 lower alkyl group; R^{17} is not a hydrogen atom, C_2-C_7 alkoxycarbonyl group, or C_1-C_6 hydroxyalkyl group; r is not 0 and A^3 is not a single bond or -CO-;

With the further proviso that when R^3 is a hydrogen atom and k represents 2, R^7 is not unsubstituted; m is not 0 and R^{11} is not a substituted or unsubstituted phenyl group;

and, when R^3 is a cyano group, R^7 is not unsubstituted, and the substituent groups for R^7 are not a halogen atom, C_1-C_6 lower alkyl group or C_1-C_6 lower alkoxy group.

2. A compound as set forth in Claim 1, wherein k is 3 in formula [I].

3. A compound as forth in Claim 1 wherein j is 2 in formula [I].

4. A compound as set forth in Claim 1, wherein R^3 is a hydrogen atom in formula [I].

5. A compound as set forth in Claim 1, in which R^3 is a hydroxy group in formula [I].

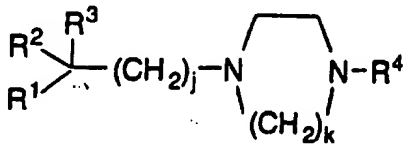
6. A compound as set forth in Claim 1, wherein R^1 and R^2 are the same or different from each other and are substituted or unsubstituted phenyl groups in formula [I].

7. A compound as set forth in Claim 1, wherein R^4 in formula [I] is a group represented by the formula: $-CH_2-R^7$ wherein R^7 is as defined for R^7 in formula [I].

8. A compound as set forth in Claim 1, wherein R^4 is $-CH_2-CO-NH-NH-CO-R^7$, $-CH_2-CO-NH-NH-CO-CH_2-R^7$, $-CH_2-CO-NH-NH-CO-NH-R^7$, $-CH_2-CO-NH-CH_2-CO-R^7$, $-CH_2-CO-NH-NH-CO-R^{20}$, $-CH_2-CO-NH-NH-CO-NH-R^{20}$, or $-CH_2-CO-NH-CH_2-CO-R^{20}$ where R^7 and R^{20} are as defined in formula [I].

9. A meth d of inhibiting the binding of chemokines to the receptor of a target cell and/or its action on a target cell using a pharmaceutical

preparation containing as an effective ingredient, a cyclic diamine, or its pharmacologically acceptable acid addition salt, represented by the formula [II] below:



[II]

wherein R^1 and R^2 are the same or different from each other and are a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, nitrogen atoms or combinations thereof, in which the phenyl or aromatic heterocyclic group may be substituted by one or more halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, C_1-C_6 hydroxyalkyl groups, carboxy groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoylamino groups, dioxolanyl groups, or by group represented by the formula: $-NR^5R^6$, or is condensed with a benzene ring to form a condensed ring, wherein the substituents for the phenyl or aromatic heterocyclic group and the condensed ring condensed with a benzene ring are optionally substituted by one or more substituents independently selected from halogen atoms, hydroxy groups, or C_1-C_6 lower alkoxy groups, and R^5 and R^6 are the same or different from each other and are hydrogen atoms, C_1-C_6 lower alkyl groups, or C_2-C_6 lower alkenyl groups;

R^3 is a hydrogen atom, hydroxy group, cyano group, C_1-C_6 lower alkoxy group or C_2-C_7 lower alkanoyloxy group;

j represents an integer of 0-3;

k represents 2 or 3;

R^4 is a group represented by:

1) $-A^1-R^7$

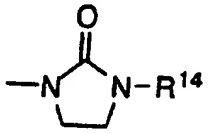
wherein R^7 is an unsubstituted or substituted phenyl group which may be substituted by one or more groups which are the same or different and are halogen atoms, hydroxy groups, amino groups, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyl groups, C_1-C_6 alkylsulfonyl groups, trifluoromethylsulfonyl groups, unsubstituted phenylsulfonyl groups or substituted with a hydroxy group, 1-pyrrolylsulfonyl groups, C_1-C_6 hydroxyalkylsulfonyl groups, C_1-C_6 alkanoylamino groups, or a group of the formula: $-CONR^8R^9$ in which R^8 and R^9 are the same or different from each other,

and are hydrogen atoms or C_1-C_6 lower alkyl groups; A^1 is a gr up of the f rmula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G is G^1 or G^2; wherein G^1 represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$; and G^2 represents $-(C=NH)NH-SO_2-$, -CO-NH-NH-CO-, -CO-NH-NH-CO-NR^{10}-, -CO-NH-CH_2-CO-, -CO-NH-NH-SO_2-, or -CO-N(CH_2-CO-OCH_3)-NH-CO-; R^{10} is a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; q represents 0 or 1;

2) $-A^2-R^{11}$

wherein A^2 is -CO- or $-SO_2-$; R^{11} is;

a) an unsubstituted or substituted phenyl group which is substituted by one or more groups which are the same or different and are halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



b) an aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, nitrogen atoms or combinations thereof, which may be substituted with one or more of the same or different groups which are halogen atoms, C_1-C_6 lower alkyl groups, or C_1-C_6 lower alkoxy groups, or

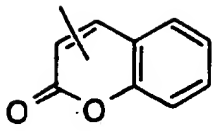
c) A group represented by the formula: $-CH_2-NR^{15}R^{16}$,

where R^{12}, R^{13}, R^{14} and R^{15}, are the same or different groups, and are hydrogen atoms or C_1-C_6 lower alkyl groups and R^{16} is a phenyl group or a phenylalkyl group, which may be substituted by one or more of the same or different groups which are halogen atoms, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group;

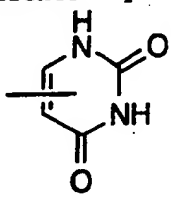
3) $-(CH_2)_n-R^{17}$

wherein R^{17} is a group which may be substituted at any possible sites by one or more of the same or different groups which are halogen atoms, hydroxy groups, C_1-C_6 lower alkyl groups, or C_1-C_6 lower alkoxy groups, representing

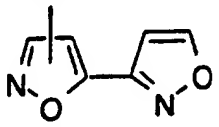
a hydrogen atom, cyano group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 hydroxyalkyl group, C_1-C_6 lower alkynyl group, C_3-C_6 cycloalkyl group, C_3-C_7 alkenoyl group, a group represented by the formula: $-(CHOH)CH_2OR^{18}$, a group represented by the formula: -CO-NH-NH-CO-OR^{19}, a group represented by the formula:



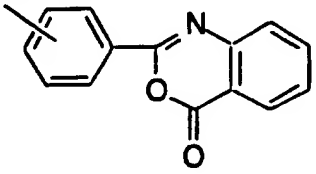
a group represented by the formula:



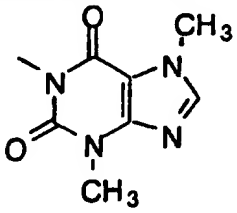
a group represented by the formula:



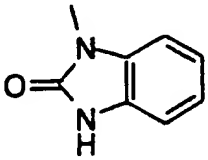
a group represented by the formula:



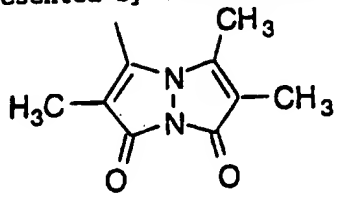
a group represented by the formula :



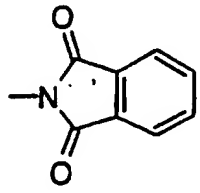
a group represented by the formula:



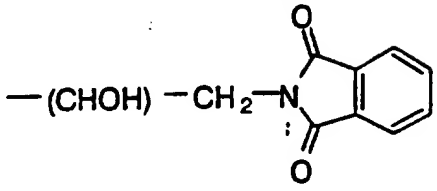
a group represented by the formula:



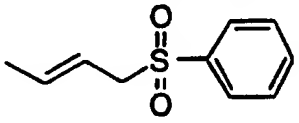
a group represented by the formula:



a group represented by the formula:

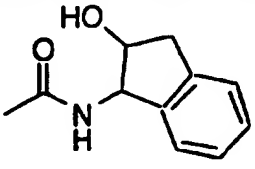


a group represented by the formula:



, or

a group represented by the formula:



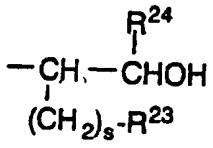
in which n is an integer of 1-4; R^{18} is a C_1-C_6 lower alkyl group, C_2-C_6 lower alkenyl group, or C_2-C_6 lower alkynyl group and R^{19} represents a C_1-C_6 lower alkyl group;

4) $-(CH_2)_r-A^3-R^{20}$

wherein r represents an integer of 0-3; A^3 represents a single b nd, -CO-, -CO-NH-NH-CO-, -CO-NH-NH-CO-NH-, -CO-NH-CH_2-CO-, -CO-NH-NH-SO_2-, -(CHOH)-CH_2-, or -(CHOH)-CH_2OCH_2-; R^{20} represents an aromatic heterocyclic group containing 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, nitrogen atoms or combinations thereof in which the aromatic heterocyclic group may be substituted by one or more of the same or different groups which are halogen atoms, C_1-C_6 lower alkyl groups, C_1-C_6 lower alkoxy groups, or pyrrolyl groups) or is condensed with a benzene ring to form a condensed ring);

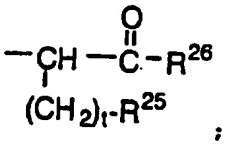
5) $-CH_2-CO-NR^{21}R^{22}$

wherein R^{21} is a hydrogen atom or C_1-C_6 lower alkyl group; R^{22} represents a hydrogen atom, C_1-C_6 lower alkyl group, or a group represented by the formula:



,or

a group represented by the formula:



;

or R^{21} and R^{22}, taken together with the nitrogen to which they are attached form a 4 to 7-membered saturated heterocycle, which may contain an oxygen atom, sulfur atom, or another nitrogen atom; where s represents 0 or 1; t represents an integer of 0-2; R^{23} represents a hydrogen atom, hydroxy group, phenyl group, C_1-C_6 lower alkyl group, or C_1-C_6 lower alkoxy group; R^{24} represents a hydrogen atom or phenyl group which may be substituted by a hydroxy group; R^{25} represents a hydrogen atom, phenyl group which may be substituted a by hydroxy group, C_2-C_7 alkoxycarbonyl group, C_1-C_6 lower alkyl group, C_1-C_6 alkylthio group, or 3-indolyl group; and R^{26} represents a hydroxy group, amino group, C_1-C_6 lower alkoxy group, or phenylalkyloxy group;

6) a hydrogen atom, C_1-C_6 alkanoyl group, or C_2-C_7 alkoxycarbonyl group.

10. A method according Claim 9, in which k is 3 in the above formula [II] or its pharmacologically acceptable acid addition salt.

11. A method according to Claim 9, where j is 2 in the above formula [II] or its pharmacologically acceptable acid addition salt.

12. A method according to Claim 9, in which R^3 is a hydrogen atom in the above formula [II] or its pharmacologically acceptable acid addition salt.

13. A method according to Claim 9, in which R^3 is a hydroxy group in the above formula [II] or its pharmacologically acceptable acid addition salt.

14. A method according to Claim 9, in which R^1 and R^2 are the same or different from each other and are substituted or unsubstituted phenyl groups in the above formula [II] or its pharmacologically acceptable acid addition salt.

15. A method according to Claim 9, in which R^4 is a group represented by the formula: $-CH_2-R^7$ where R^7 is as defined in R^7 in the above formula [II]), or its pharmacologically acceptable acid addition salt.

16. A method according to Claim 9, where R^4 is a group represented by the formula: $-CH_2-R^{20}$ wherein R^{20} is as defined in the above formula [II] or its pharmacologically acceptable acid addition salt.

17. A method according to Claim 9, wherein R^4 in the above formula [II] is $-CH_2CO-NH-NH-CO-R^7$, $-CH_2-CO-NH-NH-CO-CH_2-R^7$, $-CH_2-CO-NH-NH-CO-NH-R^7$, $-CH_2-CO-NH-CH_2-CO-R^7$, $-CH_2-CO-NH-NH-CO-R^{20}$, $-CH_2-CO-NH-NH-CO-NH-R^{20}$, or $-CH_2-CO-NH-CH_2-CO-R^{20}$, wherein in the formulas, R^7 and R^{20} are the same as defined in the above formula [II] or its pharmacologically acceptable acid addition salt.

18. A method according to Claim 9, wherein the chemokine is MIP-1a.

19. A method according to Claim 9, wherein the chemokine is MCP-1.

20. A method according to Claim 9 wherein the chemokine is IL-8.

INTERNATIONAL SEARCH REPORT

Inter inal Application No
PCT/US 97/08577

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D243/08 C07D295/14 C07D295/08 C07D295/06 C07D401/06
C07D405/06 C07D403/06 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 03371 A (BASF AKTIENGESELLSCHAFT) 5 April 1990 see the whole document	1-9
A	EP 0 166 302 A (POLIINDUSTRIA CHIMICA) 2 January 1986 see the whole document	1-9
P,A	WO 96 25157 A (SMITHKLINE BEECHAM CORPORATION) 22 August 1996 see page 99 - page 112; claims	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 1997	26.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/ 08577

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 9-20 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 97/08577

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9003371 A	05-04-90	DE 3831993 A	29-03-90
		AT 131819 T	15-01-96
		CA 1337653 A	28-11-95
		DE 58909539 D	01-02-96
		EP 0435902 A	10-07-91
		JP 4501711 T	26-03-92
		US 5342839 A	30-08-94
EP 166302 A	02-01-86	JP 61017574 A	25-01-86
WO 9625157 A	22-08-96	NONE	